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FOR

ANTIVIRAL AZAINDOLE DERIVATIVES

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ANTIVIRAL AZAINDOLE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Non-Provisional Application Serial Number 09/765,189 filed January 18, 2001 and U.S. Provisional Application Serial Number 60/184,004 filed February 22, 2000.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with azaindole piperazine diamide derivatives that possess unique antiviral activity. More particularly, the present invention relates to compounds useful for the treatment of HIV and AIDS.

Background Art

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 33.6 million people infected worldwide. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 1999, 5.6 million new infections were reported, and 2.6 million people died from AIDS. Currently available drugs for the treatment of HIV include six nucleoside reverse transcriptase (RT) inhibitors (zidovudine, didanosine, stavudine, lamivudine, zalcitabine and abacavir), three non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine and efavirenz), and five peptidomimetic protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir and amprenavir). Each of these drugs can only transiently

restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present (Larder and Kemp; Gulick; Kuritzkes; Morris-Jones *et al*; Schinazi *et al*; Vacca and Condra; Flexner; Berkhout and Ren *et al*; (Ref. 6-14)). Therefore, novel anti-HIV agents exhibiting distinct *resistance patterns, and favorable pharmacokinetic as well as safety* profiles are needed to provide more treatment options.

Currently marketed HIV-1 drugs are dominated by either nucleoside reverse transcriptase inhibitors or peptidomimetic protease inhibitors. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have recently gained an increasingly important role in the therapy of HIV infections (Pedersen & Pedersen, Ref. 15). At least 30 different classes of NNRTI have been described in the literature (De Clercq, Ref. 16) and several NNRTIs have been evaluated in clinical trials. Dipyridodiazepinone (nevirapine), benzoxazinone (efavirenz) and bis(heteroaryl) piperazine derivatives (delavirdine) have been approved for clinical use. However, the major drawback to the development and application of NNRTIs is the propensity for rapid emergence of drug resistant strains, both in tissue cell culture and in treated individuals, particularly those subject to monotherapy. As a consequence, there is

considerable interest in the identification of NNRTIs less prone to the development of resistance (Pedersen & Pedersen, Ref. 15).

Several indole derivatives including indole-3-sulfones, piperazino indoles, pyrazino indoles, and 5H-indolo[3,2-b][1,5]benzothiazepine derivatives have been reported as HIV-1 reverse transciptase inhibitors (Greenlee et al, Ref. 1; Williams et al, Ref. 2; Romero et al, Ref. 3; Font et al, Ref. 17; Romero et al, Ref. 18; Young et al, Ref. 19; Genin et al, Ref. 20; Silvestri et al, Ref. 21). Indole 2-carboxamides have also been described as inhibitors of cell adhesion and HIV infection (Boschelli et al, US 5,424,329, Ref. 4). Finally, 3-substituted indole natural products (Semicochliodinol A and B, didemethylasterriquinone and isocochliodinol) were disclosed as inhibitors of HIV-1 protease (Fredenhagen et al, Ref. 22).

Structurally related aza-indole amide derivatives have been disclosed previously (Kato et al, Ref. 23; Levacher et al, Ref. 24; Mantovanini et al, Ref. 5(a); Cassidy et al, Ref. 5(b); Scherlock et al, Ref. 5(c)). However, these structures differ from those claimed herein in that they are aza-indole mono-amides rather than unsymmetrical aza-indole piperazine diamide derivatives, and there is no mention of the use of these compounds for treating antiviral infections, particularly HIV. Nothing in these references can be construed to disclose or suggest the novel compounds of this invention and their use to inhibit HIV infection.

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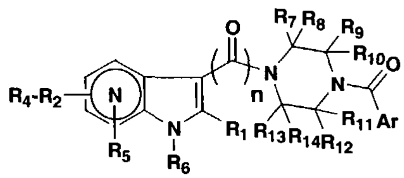
SUMMARY OF THE INVENTION

The present invention comprises compounds of Formula I, or pharmaceutically acceptable salts thereof, which are effective antiviral agents, particularly as inhibitors of HIV.



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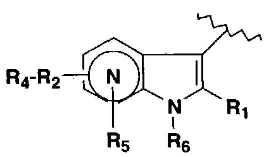
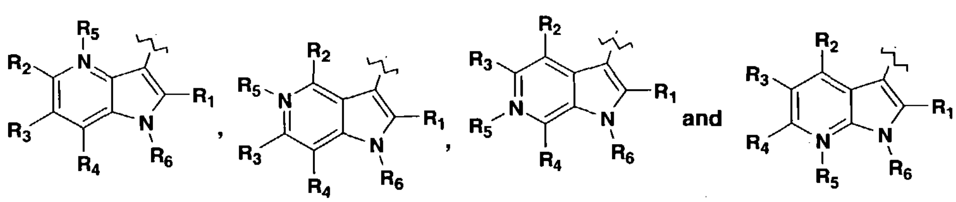
 is selected from the group consisting of



R_1, R_2, R_3, R_4 are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, C_2-C_6 alkynyl, halogen, CN, phenyl, nitro, $OC(O)R_{15}$, $C(O)R_{15}$, $C(O)OR_{16}$, $C(O)NR_{17}R_{18}$, OR_{19}, SR_{20} and $NR_{21}R_{22}$;

R_{15}, is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl and C_4-C_6 cycloalkenyl;

R_{16}, R_{19}, and R_{20} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_{1-6} alkyl substituted with one to three

halogen atoms, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the oxygen or sulfur to which R_{16}, R_{19}, or R_{20} is attached;

R_{17} and R_{18} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_4-C_6 cycloalkenyl and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_6 alkenyl or the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{17} and R_{18} is attached;

R_{21} and R_{22} are each independently selected from the group consisting of H, OH, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_5-C_6 cycloalkenyl, C_3-C_6 alkynyl and $C(O)R_{23}$; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_6 alkenyl, C_4-C_6 cycloalkenyl, or the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{21} and R_{22} is attached;

R_{23} is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_2-C_6 alkynyl;

R_5 is $(O)_m$, wherein m is 0 or 1;

n is 1 or 2;

R_6 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_4-C_6 cycloalkenyl, $C(O)R_{24}$, $C(O)OR_{25}$, $C(O)NR_{26}R_{27}$, C_3-C_6 alkenyl and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_6 alkenyl or the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_6 is attached;

R_{24} is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_3-C_6 alkynyl;

R_{25} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6alkynyl are not the point of attachment to the oxygen to which R_{25} is attached;

R_{26} and R_{27} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_5-C_6 cycloalkenyl, and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_6 alkenyl, C_5-C_6 cycloalkenyl, or the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{26} and R_{27} are attached;

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, C_2-C_6 alkynyl, $CR_{28}R_{29}OR_{30}$, $C(O)R_{31}$, $CR_{32}(OR_{33})OR_{34}$, $CR_{35}NR_{36}R_{37}$, $C(O)OR_{38}$, $C(O)NR_{39}R_{40}$, $CR_{41}R_{42}F$, $CR_{43}F_2$ and CF_3;

R_{28}; R_{29}, R_{30}, R_{31}, R_{32}, R_{35}, R_{41}, R_{42} and R_{43} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, C_2-C_6 alkynyl and $C(O)R_{44}$;

R_{33}, R_{34} and R_{38} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the oxygen to which R_{34} and R_{38} are attached;

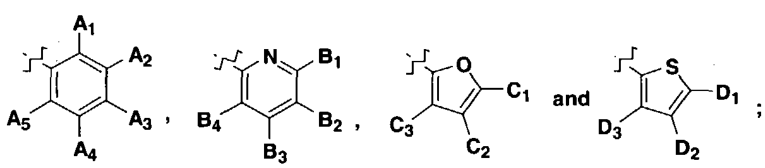
R_{36} and R_{37} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_4-C_6 cycloalkenyl, and

C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{36} and R_{37} are attached;

R_{39} and R_{40} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{39} and R_{40} are attached;

R_{44} is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, and C_2-C_6 alkynyl;

Ar is selected from the group consisting of



A_1, A_2, A_3, A_4, A_5, B_1, B_2, B_3, B_4, C_1, C_2, C_3, D_1, D_2, and D_3 are each independently selected from the group consisting of H, CN, halogen, NO_2, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, C_2-C_6 alkynyl, OR_{45}, $NR_{46}R_{47}$, SR_{48}, N_3 and $CH(-N{=}N-)-CF_3$;

R_{45} is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl and C_3-C_6 alkynyl; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the oxygen to which R_{45} is attached;

R_{46} and R_{47} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl, C_5-C_6 cycloalkenyl,

C_3-C_6 alkynyl and $C(O)R_{50}$; provided the carbon atoms which comprise the carbon-carbon double bond of said C_5-C_6 alkenyl, C_4-C_6 cycloalkenyl, or the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the nitrogen to which R_{46} and R_{47} are attached;

R_{48} is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_4-C_6 cycloalkenyl, C_3-C_6 alkynyl and $C(O)R_{49}$; provided the carbon atoms which comprise the carbon-carbon triple bond of said C_3-C_6 alkynyl are not the point of attachment to the sulfur to which R_{48} is attached;

R_{49} is C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

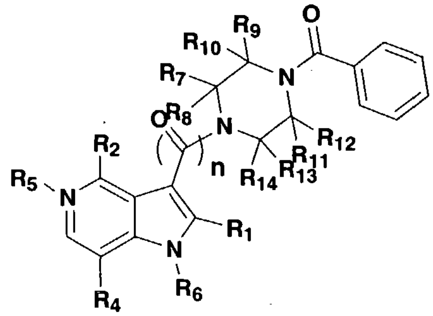
R_{50} is selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

Preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein R_2-R_4 is independently H, $-OCH_3$, $-OCH_2CF_3$, -OiPr, -OnPr, halogen, CN, NO_2, C_1-C_6 alkyl, NHOH, NH_2, Ph, SR_{20}, or $N(CH_3)_2$.

Also preferred are compounds of Formula I wherein one or two of R_7-R_{14} is independently methyl and the other substituents are hydrogen.

Also preferred are compounds of Formula I wherein one of A_1-A_5, B_1-B_4, C_1-C_3 or D_1-D_3 are either hydrogen, halogen, or amino and the remaining substituents are hydrogen.

Also preferred are compounds of the formula below:



wherein:

R_2 is H, F, Cl, Br, OMe, CN, or OH;

R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, Cl, OMe, CN, OH, $C(O)NH_2$, C(O)NHMe, C(O)NHEt, Ph or $-C(O)CH_3$;

n is 2;

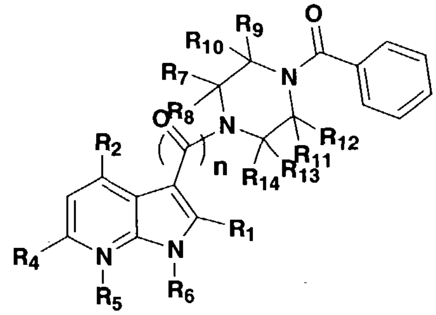
R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each independently H or CH3, provided up to two of these substituents may be methyl;

R_1 is hydrogen;

R_5 is unsubstituted; and

R_6 is hydrogen or methyl.

A most preferred aspect of the invention are compounds or pharmaceutically acceptable salts thereof of the Formula



wherein:

R_2 is H, $-OCH_3$, $-OCH_2CF_3$, -OPr, halogen, CN, NO_2, or NHOH;

R_4 is H, -halogen, -CN, or hydroxy;

One or two members of R_7-R_{14} is methyl and the remaining members are hydrogen;

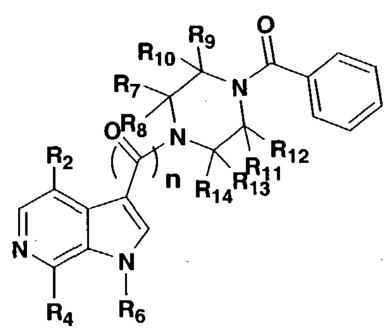
n is 2;

R_1 is hydrogen;

R_5 is $(O)_m$, where m is O; and

R_6 is hydrogen, methyl, or allyl.

Another most preferred aspect of the invention are compounds of the formula below wherein:



wherein:

R_2 is selected from the group consisting of H, F, Cl, Br, OMe, CN, and OH;

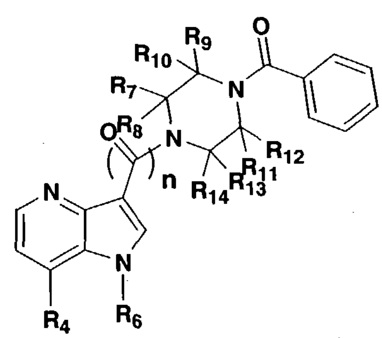
R_4 is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, Cl, OMe, CN, OH, $C(O)NH_2$, C(O)NHMe, C(O)NHEt, phenyl and $-C(O)CH_3$;

n is 2;

R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H or CH_3, provided 0-2 of the members of the group R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} may be CH_3 and the remaining members of the group R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are H; and

R_6 is H or CH_3.

Another most preferred aspect of the inventions are compounds of formula:



wherein:

R_4 is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, Cl, OMe, CN, OH, $C(O)NH_2$, C(O)NHMe, C(O)NHEt, phenyl and $-C(O)CH_3$;

n is 2;

R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H or CH_3, provided 0-2 of the members of the group R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} may be CH_3 and the remaining members of the group R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are H; and

R_6 is H or CH_3.

Since the compounds of the present invention, may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present invention includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I.

Another embodiment of the invention is a pharmaceutical composition which comprises an antiviral effective amount of a compound of Formula I.

Another embodiment of the present invention is a method for treating mammals infected with a virus, wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I.

Another embodiment of the present invention is a method for treating mammals infected with a virus, such as HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an

AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

The preparative procedures and anti-HIV-1 activity of the novel azaindole piperazine diamide analogs of Formula I are summarized below. The definition of various terms follow.

The term "C_{1-6} alkyl" as used herein and in the claims (unless the context indicates otherwise) means straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like. Similarly, "C_{1-6} alkenyl" or "C_{1-6} alkynyl" includes straight or branched chain groups.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

Physiologically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or

tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

In the method of the present invention, the term "antiviral effective amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with HIV infection.

The present invention is also directed to combinations of the compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)

Amprenivir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC

AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	Sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic

ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)

HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)

Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC

VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNOMODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS

Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma

Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP

Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal Meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT Therapy

Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of Anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption Related to AIDS

Additionally, the compounds of the invention herein may be used in combinations which include more than three anti HIV drugs. Combinations of four or even five HIV drugs are being investigated and the compounds of this invention would be expected to be a useful component of such combinations.

Additionally, the compounds of the invention herein may be used in combination with another class of agents for treating AIDS which are called HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV

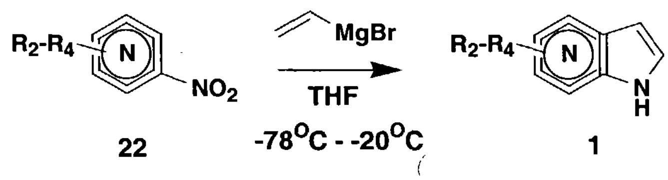
protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Finally a new protease inhibitor , BMS-232632, which is currently undergoing clinical trials may become a preferred inhibitor. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

Parent azaindoles such as 4-azaindole, 5-azaindole, 6-azaindole, or 7-azaindole are prepared by the methods described in the literature (Mahadevan et al, Ref. 25(a)) or Hands et. al. Ref 25 (b) are available from commercial sources (7-azaindole from Aldrich Co.). This reference and similar references show some examples of substituted aza indoles.

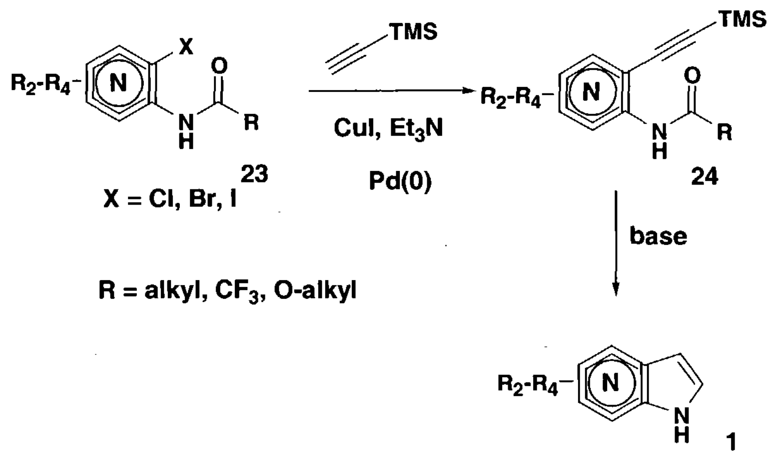
Chemist skilled in the art can recognize that the general methodology can be extended to azaindoles which have different substituents in the starting materials. Azaindoles are also prepared *via* the routes described in Scheme 1 and Scheme 2.

Scheme 1



In Scheme 1, the Bartoli indole synthesis (Dobson et al, Ref. 25 (C)) is extended to prepare substituted azaindoles. Nitropyridine **22** was reacted with an excess of vinyl magnesium bromide at -78^{O}C. After warming up to -20^{O}C, the reaction provides the desired azaindole **1**. Generally these temperature ranges are optimal but in specific examples may be varied usually by no more than 20 ^{O}C but occasionally by more in order to optimize the yield. The vinyl magnesium bromide may be obtained commercially as a solution in tetrahydrofuran or sometimes more optimally may be prepared fresh from vinyl bromide and magnesium using literature procedures which are well known in the art. Vinyl magnesium chloride can also be used in some examples.

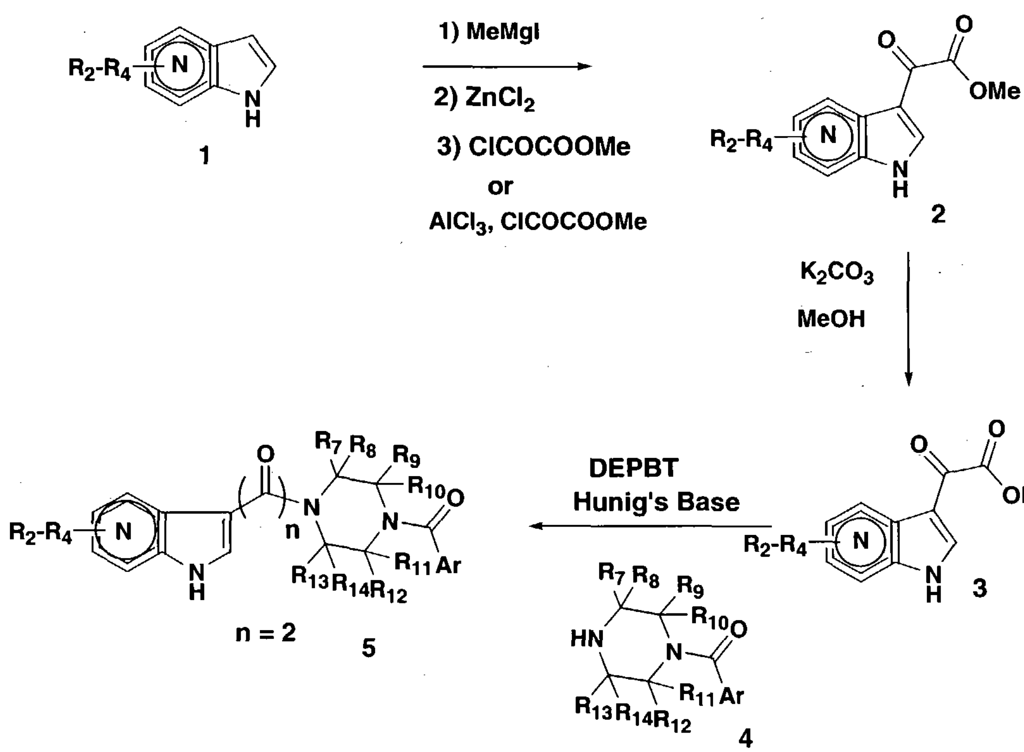
Scheme 2



In Scheme 2, acetylene is coupled onto a halo-pyridine **23** using a Pd (0) catalyst to furnish **24**. Subsequent treatment with base effects cyclization of **24** to afford azaindole **1**(Sakamoto et al, Ref. 26). Suitable bases for the second step include sodium methoxide or other sodium, lithium, or potassium alkoxide bases.

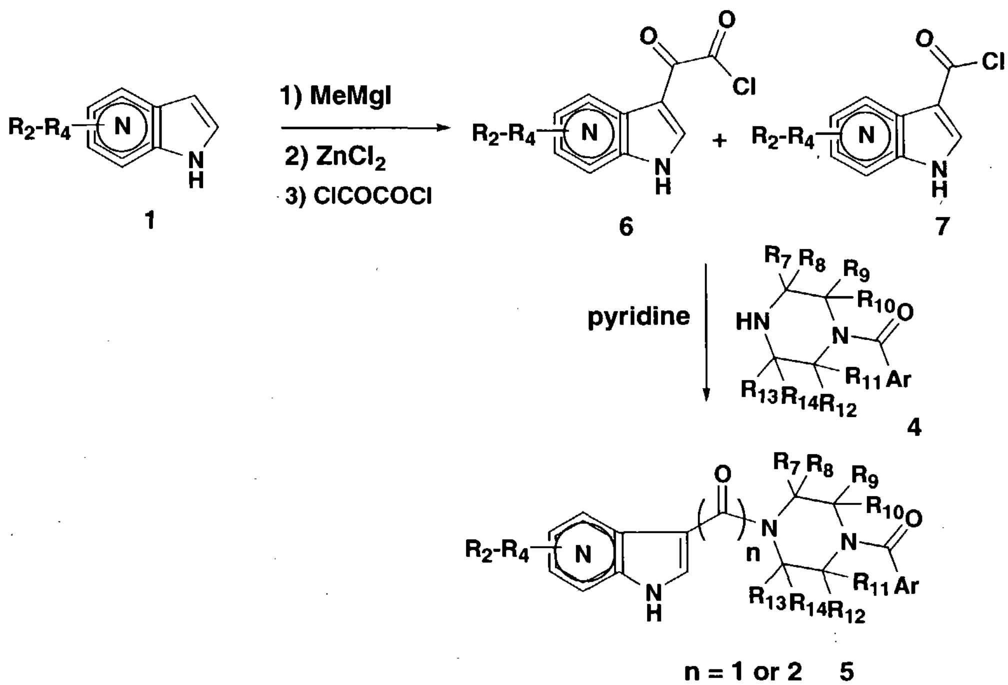
General procedures to prepare azaindole piperazine diamide **5** of Formula I are described in Scheme 3 and Scheme 4.

Scheme 3



An azaindole **1**, was reacted with MeMgI (methyl magnesium iodide) and $ZnCl_2$ (zinc chloride), followed by the addition of ClCOCOOMe (methyl chlorooxoacetate) to afford aza-indole glyoxyl methyl ester **2** (Shadrina et al, Ref. 27). Alternatively, compound **2** can be prepared by reaction of aza-indole **1** with an excess of ClCOCOOMe in the presence of $AlCl_3$ (aluminum chloride) (Sycheva et al, Ref. 28). Hydrolysis of the methyl ester **2** affords a potassium salt **3** which is coupled with mono-benzoylated piperazine derivatives **4** in the presence of DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, to provide azaindole piperazine diamide **5** (Li et al, Ref. 29). The mono-benzoylated piperazine derivatives **4** can be prepared according to well established procedures such as those described by Desai et al, Ref. 30(a), Adamczyk et al, Ref. 30(b), Rossen et al, Ref. 30(c), and Wang et al, 30(d) and 30(e).

Scheme 4

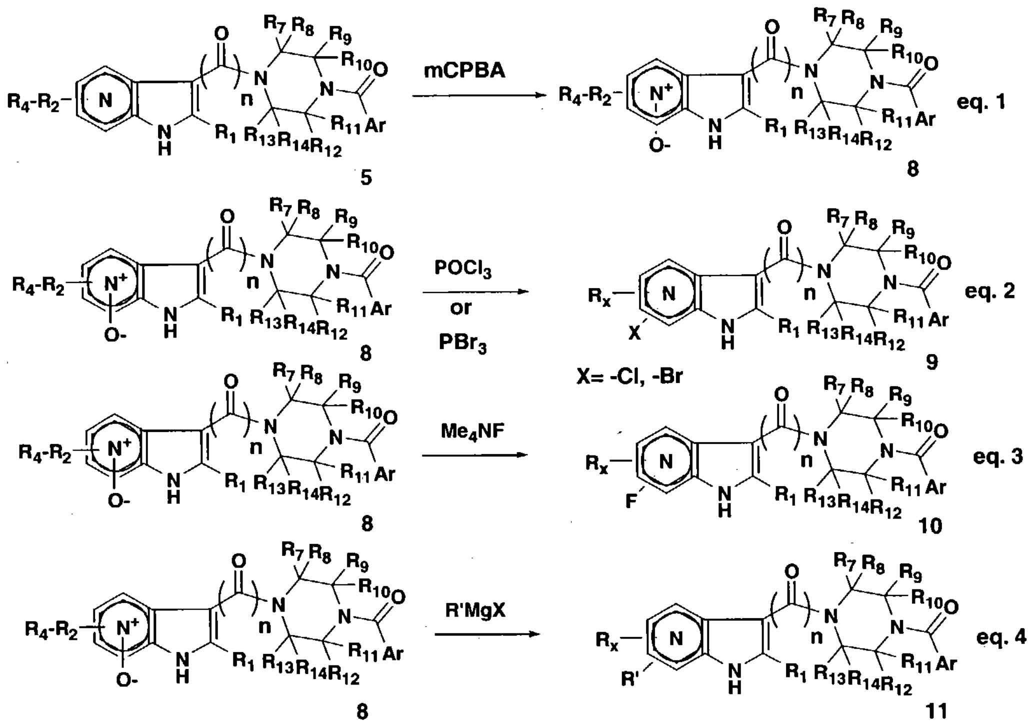


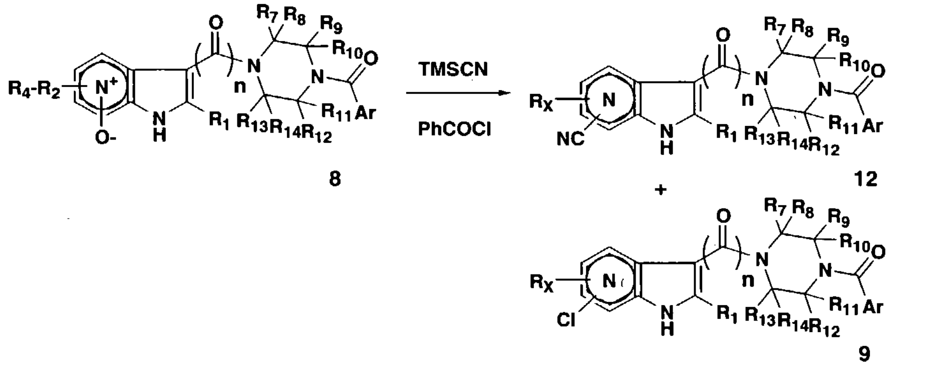
An alternative method for the preparation of **5** involves treating an azaindole **1**, obtained by procedures described in the literature or from commercial sources, with MeMgI and $ZnCl_2$, followed by the addition of ClCOCOCl (oxalyl chloride) in either THF (tetrahydrofuran) or ether to afford a mixture of desired products, glyoxyl chloride **6** and acyl chloride **7**, Scheme 4. The resulting mixture of glyoxyl chloride **6** and acyl chloride **7** is then coupled with mono-benzoylated piperazine derivatives **4** under basic conditions to afford product **5** as a mixture of two compounds (n = 1 and 2).

General routes for further functionalizing azaindole rings are shown in Schemes 5. It should be recognized that the symbol Rx is meant to represent a general depiction of the remaining substituents from R_4-R_2 which are on the azaindole ring. As depicted in Scheme 5, the azaindole can be oxidized to the corresponding *N*-oxide derivative **8** by using mCPBA (meta-Chloroperbenzoic Acid) in acetone or DMF (Dimethylformamide) (eq. 1, Harada et al, Ref. 31 and Antonini et al, Ref.

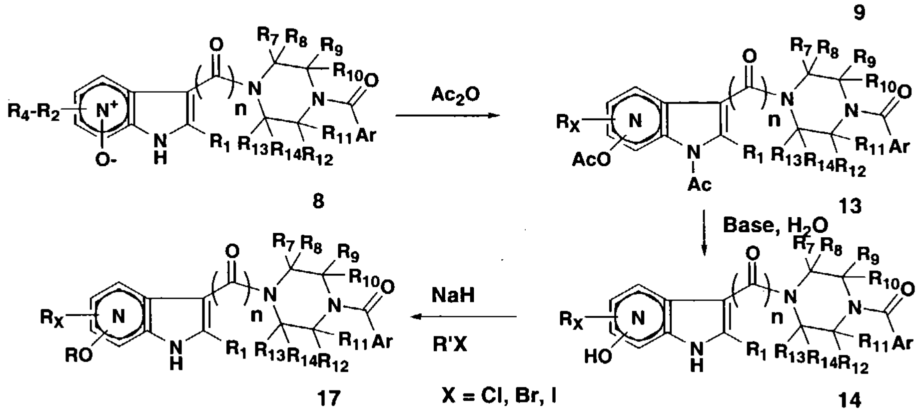
32). The *N*-oxide **8** can be converted to a variety of substituted azaindole derivatives by using well documented reagents such as phosphorus oxychloride ($POCl_3$) (eq. 2, Schneller et al, Ref. 33(a)) or phosphorus tribromide (eq. 2, Wozniak et al, Ref. 33(b)), Grignard reagents RMgX (R = alkyl, X = Cl, Br or I) (eq. 4, Shiotani et al, Ref. 34), trimethylsilyl cyanide (TMSCN) (eq. 5, Minakata et al, Ref. 35), Ac_2O (eq. 6, Klemm et al, Ref. 36), thiol via a sodium thiolate or other thiolates (eq. 7, Shiotani et al, Ref. 37), alcohol via metal alkoxides as in ref 37 or (eq. 8, Hayashida et al, Ref. 38), and amine (eq. 9, using ammonia or an amine in the presence of TsCl in chloroform / water as in Miura et al, Ref. 39; or under similar conditions but with 10% aq NaOH also included as in Solekhova et al, Ref. 40). Under such conditions (respectively), a chlorine or bromine atom, nitrile group, alkyl group, hydroxyl group, thiol group, alkoxy group and amino group can be introduced to the pyridine ring. Similarly, tetramethylamonnium fluoride (Me_4NF) transforms N-oxides **8** to fluoro-azaindoles (eq. 3). Further standard modification of OH group will provide alkoxy functionality as well (eq. 6).

Schem 5

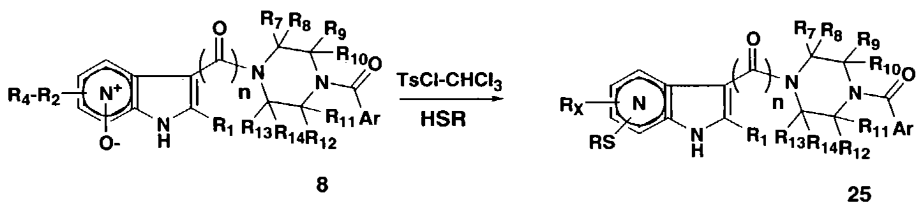




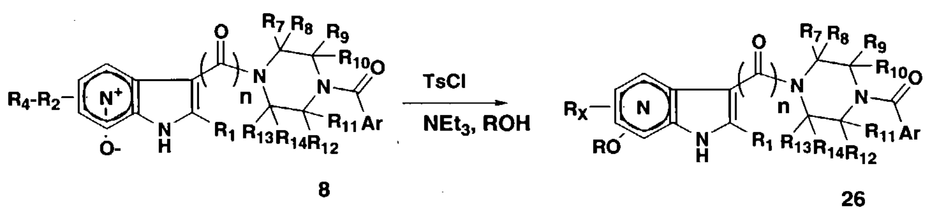
eq. 5



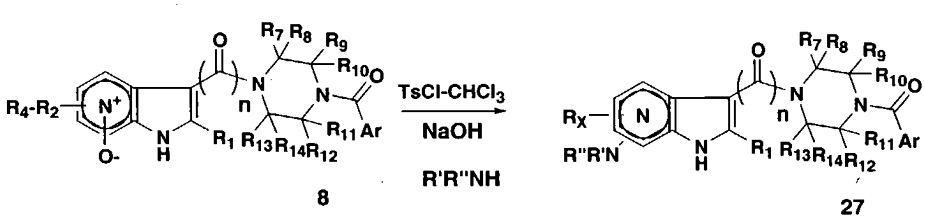
eq. 6



eq. 7



eq. 8

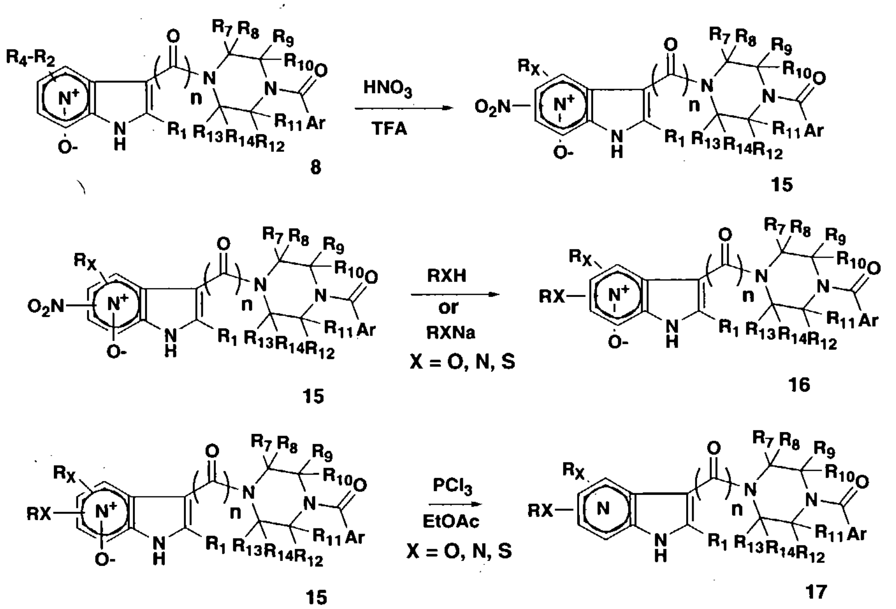


eq. 9

Nitration of azaindole *N*-oxides results in introduction of a nitro group to azaindole ring, as shown in Scheme 6 (eq. 10, Antonini et al, Ref. 32). The nitro group can subsequently be displaced by a variety of nucleophilic agents, such as OR, NR^1R^2 or SR, in a well established

chemical fashion (eq. 11, Regnouf De Vains et al, Ref. 41(a), Miura et al, Ref. 41(b), Profft et al, Ref. 41(c)). The resulting N-oxides **16** are readily reduced to the corresponding azaindole **17** using phosphorus trichloride (PCl_3) (eq. 12, Antonini et al, Ref. 32 and Nesi et al, Ref. 42) or other reducing agents. Similarly, nitro-substituted *N*-oxide **15** can be reduced to the azaindole **18** using phosphorus trichloride (eq. 13). The nitro group of compound **18** can be reduced to either a hydroxylamine (NHOH) (eq. 14, Walser et al, Ref. 43(a) and Barker et al, Ref. 43(b)) or an amino (NH_2) group (eq. 15, Nesi et al , Ref. 42 and Ayyangar et al, Ref. 44) by carefully selecting different reducing conditions.

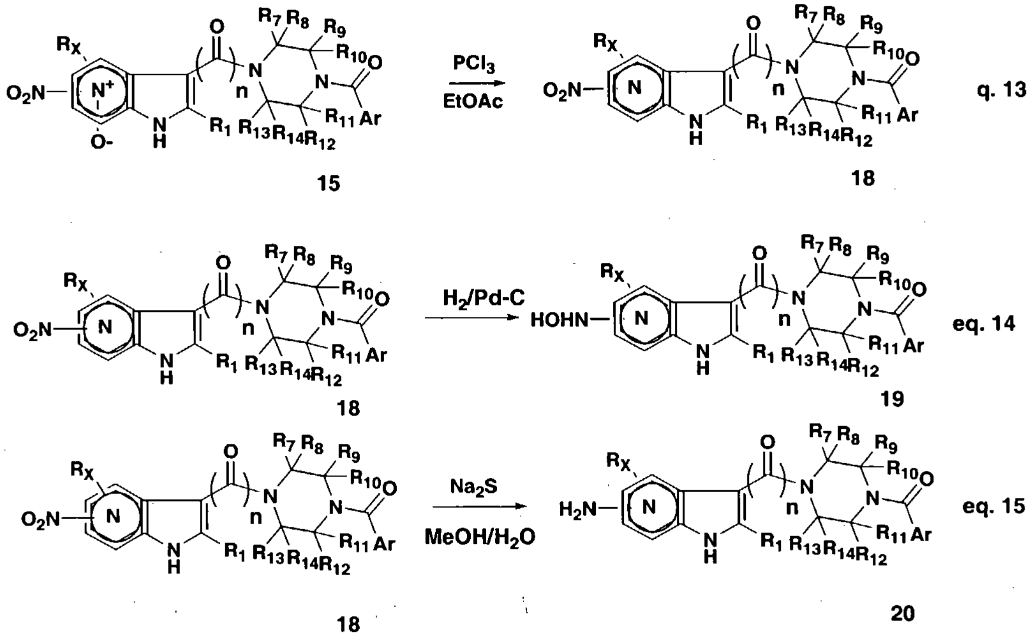
Scheme 6



eq. 10

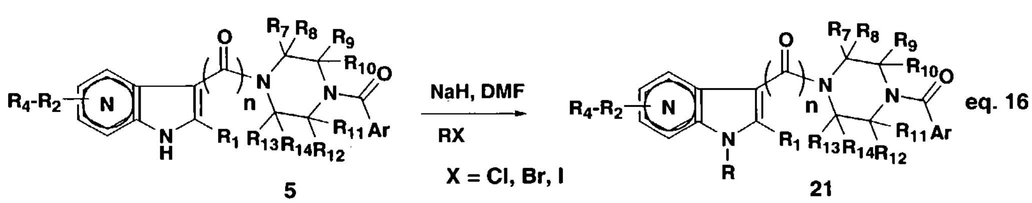
eq. 11

eq. 12



The alkylation of the nitrogen atom at position 1 of the azaindole derivatives can be achieved using NaH as the base, DMF as the solvent and an alkyl halide or sulfonate as alkylating agent, according to a procedure described in the literature (Mahadevan et al, Ref. 45) (eq. 16, Scheme 7).

Scheme 7

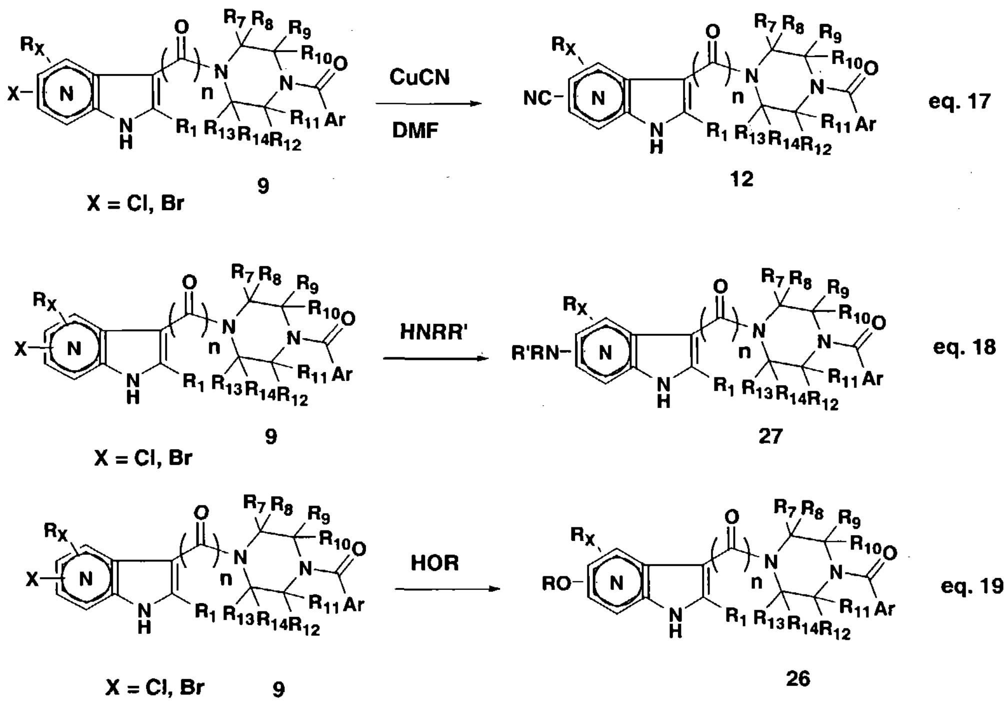


Halides can be converted to a variety of functionalities such as a nitrile (eq. 17), an amino group (eq. 18), and or an alkoxy group (eq. 19) (Scheme 8) using well established procedures. Examples of these types of transformations as depicted in eq.17 are shown in Sakamoto et al (Ref. 46 (a) in which a copper cyanide is used to form a nitrile from a halide, Halley et al (Ref. 46 (b)) which provides nitriles via copper I cyanide in

DMF, Yamaguchi et al (Ref. 46 (c)), Funhoff et al (Ref. 46 (d)) uses CuCN in NMP, Shiotani et al (Ref. 37). Typically the reaction of CuCN to displace a halide requires heating. Temperatures such as 145°C for 18h have been found to be preferred but these conditions may be varied. The temperature may be raised or lowered by up to 100°C and reaction times may vary from as little 30 minutes to as long as 80h depending on reaction temperature and substrate. As an alternative to Eq. 17, Klimesova et al uses a primary amide precursor (which can come from the carboxylic acid as described elsewhere) and phosphorus oxy chloride to generate a nitrile (Ref. 47) and Katritzky et al (Ref.48). As shown in eq 18 halides can be displaced with amines or ammonia. Some example conditions are contained in Shiotani et. al. reference 37 and in Katritzky et.al. reference 48. For example heating the halide **9** in an excess of a primary or secondary amine as solvent at a temperature of reflux (or between 20°C and 200°C) will result in displacement of the halide to provide amines **27**. In the instance of ammonia or volatile amines, a pressure reactor as described in in Katritzky et.al. reference 48 can be utilized to carry out the reaction without losing the volatile amine during heating. The reactions may be monitored by TLC or or liquid chromatography and the reaction temperature increased until reaction is observed. Cosolvents such as dioxane or pyridine may be utilized when the amine is costly. An alternative method would employ the modified palldium catalysis methods of Hartwig (Yale) or Buchwald (MIT) to effect displacement under milder conditions. As shown in eq. 19 of Scheme 8, alkoxides may be used to displace halogens in **9** and provide ethers **26**. Typically this transformation is best carried out by adding sodium to a solution of the parent alcohol to generate an alkanoate. Alternatively a strong base such as NaH, or $NaN(SiMe_3)_2$ may be employed. The corresponding lithium or potassium bases or metals may also be utilized. Usually, an excess of base with respect to the halide to be displaced is employed. Between two and twenty equivalents of alkanoate are usually used with ten being preferred. The reaction is carried out at reflux or a

temperature of between 30°C and 200°C . Typically approximately 80°C is useful. The reaction may take from four to eighty hours to reach completion with times between 12 and 48 hours being typical. As described above for eq.18, the reaction progress may be monitored. Typical conditions for displacement with sodium methoxide in methanol are provided in Shiotani et.al. reference 37 in the general procedure used for the preparation of examples 5a,5c, and 6 of the reference.

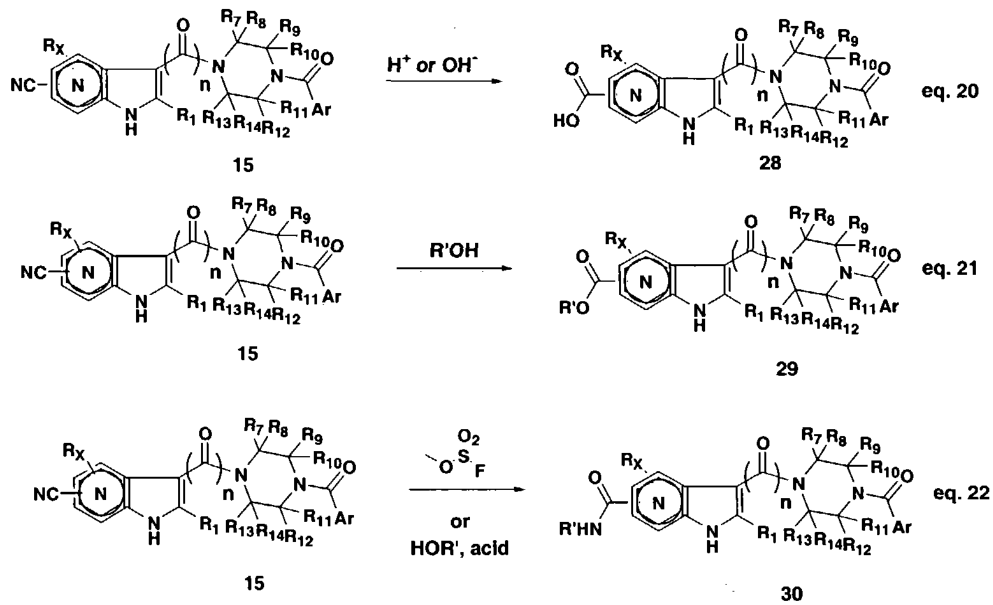
Scheme 8



The nitrile group can be converted to a carboxylic acid **28** (eq. 20, using aqueous sodium hydroxide in ethanol as in Miletin et al, Ref. 49 (a); or using KOH in aqueous ethanol as in Shiotani et al, Ref. 49 (b); or using 6N HCl as in El Hadri et al, Ref 49 (c)). The nitrile group can be converted to an ester **29** (eq. 21, using sodium methoxide in methanol as in Heirtzler et al, Ref. 50 (a); or using HCl in methanol as in Norrby et al, Ref. 50 (b)). The nitrile group can be converted to an amide **30** (eq. 22, using sulfuric acid as in Sitsun'Van et al, Ref. 51 (a); or using acetic acid, tertbutanol,

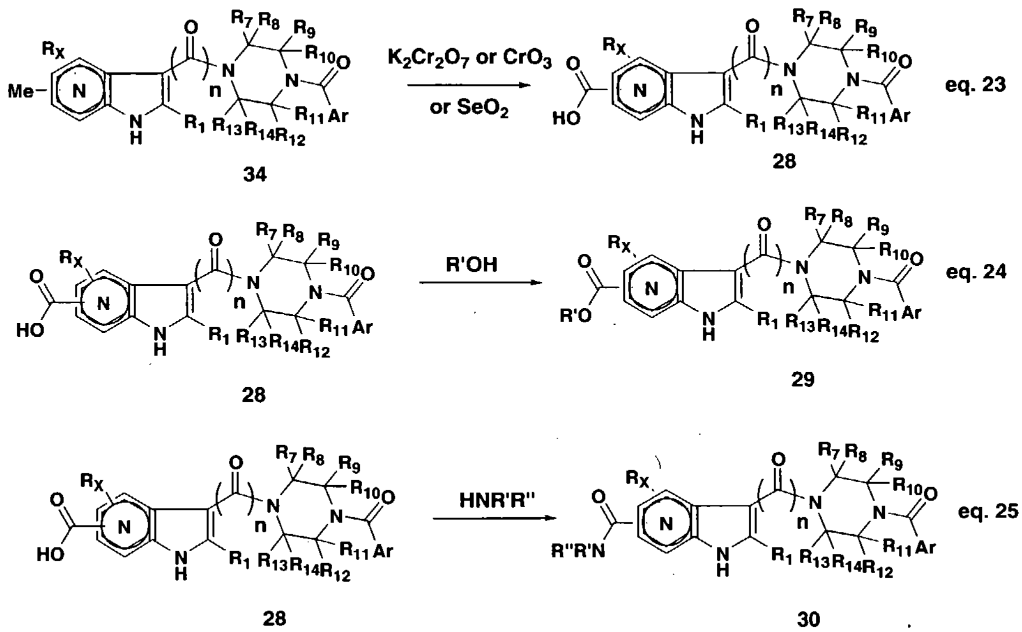
sulfuric acid, and acetonitrile as in Reich et al, 51 (b); or using $MeOS(O)_2F$ as in Salfetnikova et al, 51 (c)).

Scheme 9



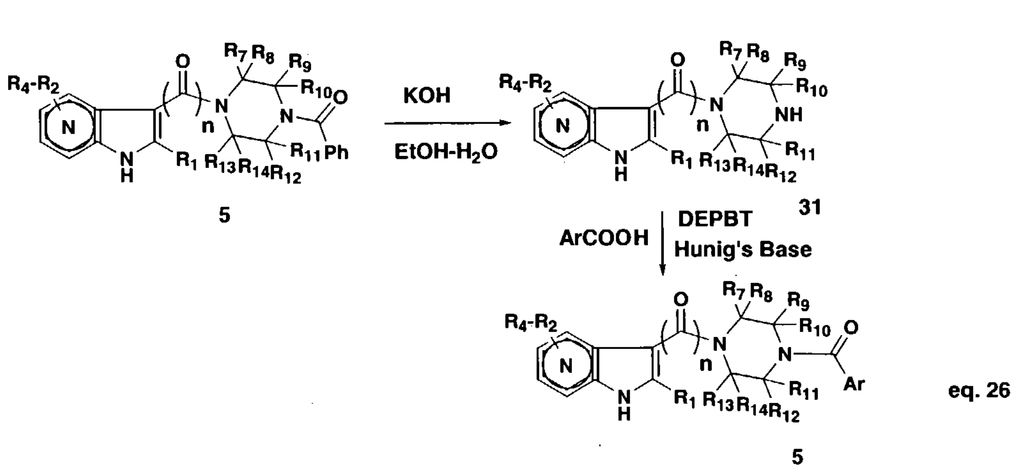
In Scheme10, the methyl group on the pyridine ring can be also oxidized to a carboxylic acid **28** using $K_2Cr_2O_7$ in 98% sulfuric acid as in (eq. 23, Oki et al, Ref. 52 (a); or using Chromium trioxide in conc sulfuric acid as in Garelli et al, Ref. 52 (b); or using selenium dioxide in pyridine as in Koyama et al, Ref. 52 (c)). The carboxylic acid may be transformed to an ester **29** using HCl in 10% methanol as in (eq. 24, Yasuda et al, Ref. 53 (a); or using thionyl chloride followed by a sodium alkyl alkoxide as in Levine et al, 53 (b); or using an alcohol and PyBOP in NMM, DMAP, and DMF as in Hoemann, 53 (c)).)). The carboxylic acid may be transformed to an amide **30** using aqueous KOH followed by oxalyl chloride in benzene followed by triethylamine in dichloromethane as in (eq. 25, Norman et al, Ref. 54 (a); or by heating an amine with the acid as in Jursic et al, 54 (b); or by coupling an amine to the acid with N,N-carbonyldiimidazole Strekowski et al, 54 (c); or by using oxalyl chloride in diethylether and an amine as in Shi et al, 54 (d)).

Scheme 10

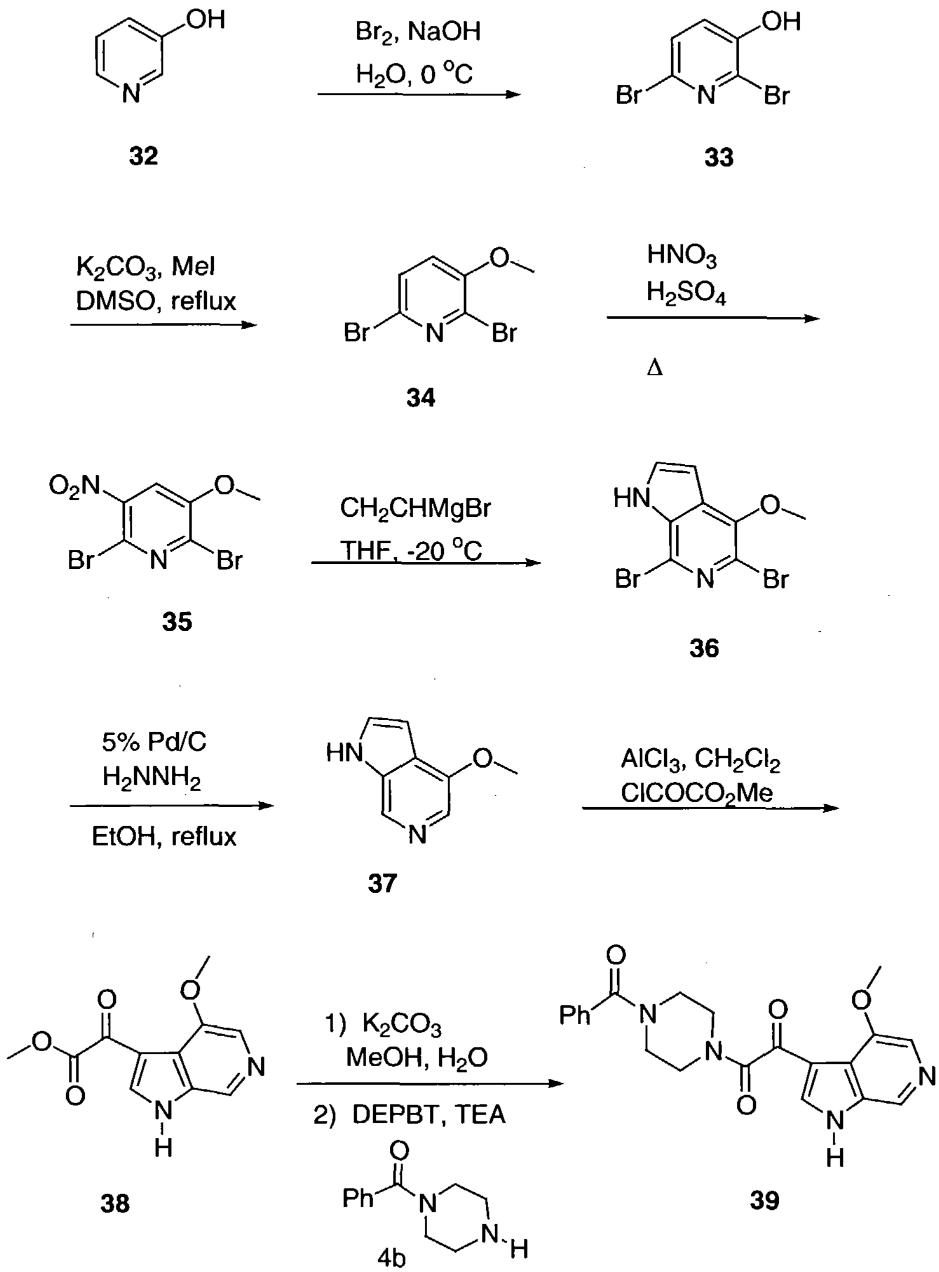


An alternative strategy for the synthesis of compounds containing varied substituents Ar is shown in Scheme 11. The benzamide moiety of the diamide **5** can be selectively hydrolyzed using to give intermediate **31**. Coupling of amine **31** with with other carboxylic acids under DEBPT and base using conditions described above for earlier couplings, provides other novel diamides **5**.

Scheme 11



Scheme 12

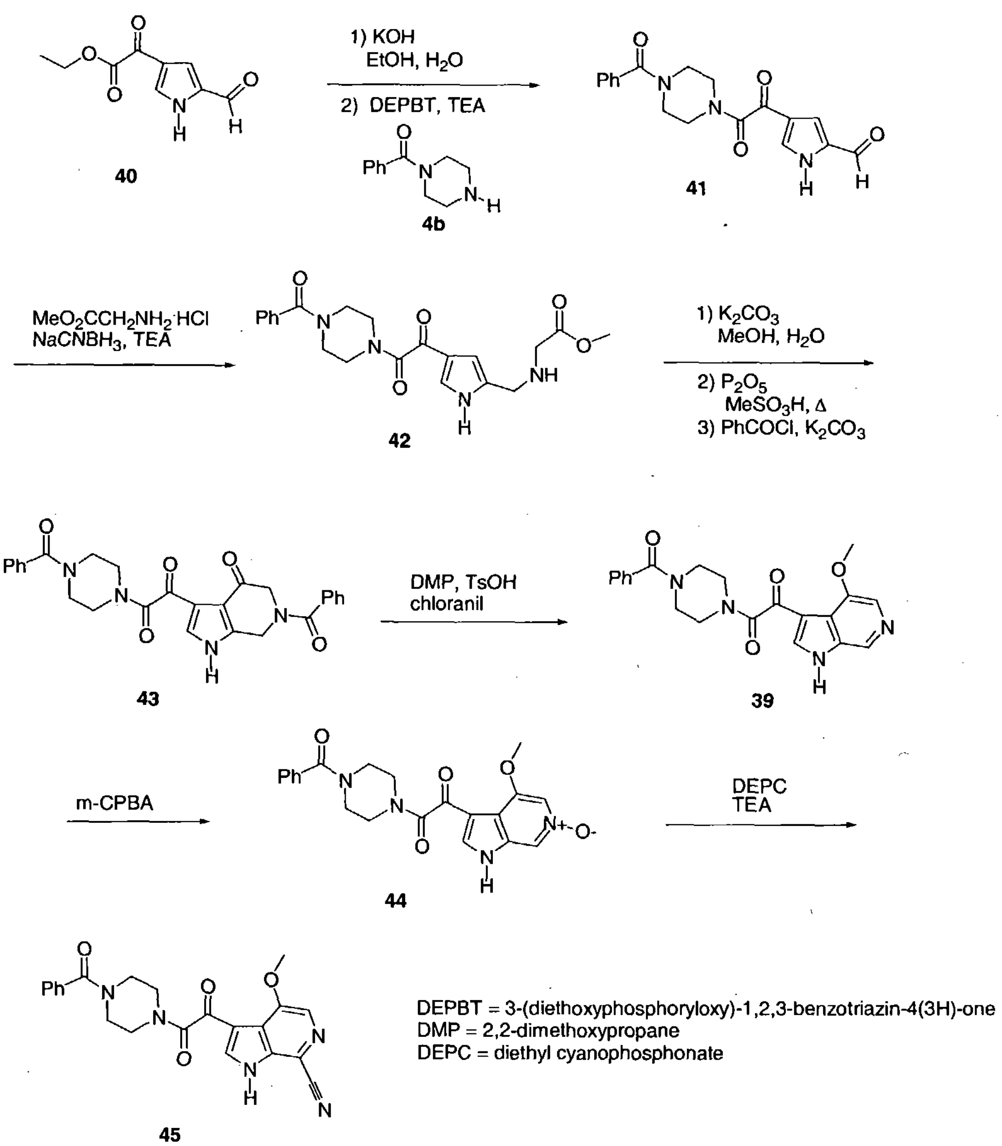


The preparation of compound **35** shown in Scheme 12 was carried out from commercially available **32** as described in Clark,G. J. ,Reference 56. The Bartoli methodology described in Scheme **1** was used to prepare 4-methoxy-6-azaindole **36.** Reduction of the bromides using transfer hydrogenation provided the desired 4-methoxy indole **37.** Compound **36** could be converted into a separable mixture of monobromides via

selective lithium bromine exchange using t-Buli at cold temperatures of between –100 to –78° followed by a quench with ammonium chloride. The alternate methodology described in Scheme 3 for acylation with chloro methyl oxalate at the 3-position was applied to **37** as shown and provided intermediate **38**. The methodology of Scheme 3 could then be followed to provide compound **39.** While the methodology in Scheme 12 is the preferred route for preparing compound **39** and other compounds of formula I, an alternative route which is depicted in Scheme 13 was developed for preparing such compounds. Pyrrole **40** was prepared via the method described in Anderson, H. J., reference 57; Hydrolysis of ester **40** using standard conditions such as potassium hydroxide in ethanol at ambient temperature for ~2h or until completion provided potassium 2-pyrrolecarboxaldehyde-4-oxoacetate. A solution of this carboxylate salt, N-benzoylpiperazine hydrochloride, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one and triethylamine in DMF was stirred for approximately one day or until completion to provide after workup and crystallization amide **41**. Amide/ aldehyde **41** was stirred as a slurry in EtOH for a short time of from 1 to 60 min., cooled to 0 °C (or between -15 and 20°) and then was stirred with glycine methyl ester hydrochloride, triethylamine (or alternatively Hunig's base, 2,6-Lutidine, or no base), and sodium cyanoborohydride to provide amine **42**. This transformation could also be carried out using aldehyde **41,** glycine methyl ester hydrochloride, and sodium triacetoxy borohydride in either dichloromethane, tetrahydrofuran, or C_1-C_4 alcohol solvents. Alternatively, the free base of glycine methyl ester could be substituted in either procedure and a dehydrating agent such as molecular sieves could be employed in the reaction prior to addition of the borohydride reducing agent. Alternatively this transformation could be carried out by first protecting the pyrrole nitrogen with a benzoyl (from benzoyl chloride and tertiary amine) or benzyl moiety (benzyl bromide, NaH or DBU in THF). The protecting groups can be removed when desired using hydrolysis with aqueous base or hydrogenation respectively. The methyl ester **42**

was hydrolyzed using potassium carbonate in methanol to provide after acidification with HCl the corresponding carboxylic acid. The acid was placed in anhydrous methanesulfonic acid containing phosphorus pentoxide which had been preheated for between 15 and 40 minutes and heated at approximately 110° (usually between 90 and 150°) for a short time of approximately 15 minutes but usually less than an hour and then poured over ice. Acylation or benzoylation of the product using for example modified Schotten-Bauman conditions (dichloromethane, potassium carbonate, and benzoyl chloride) provided ketone **43**. Reaction with dimethoxy propane and anhydrous p-toluenesulfonic acid generates an intermediate enol ether which upon reaction with chloranil provided compound **39**. The enol ether can alteratively be prepared using trimethyl ortho acetate and a sulfonic acid catalyst. Azaindoles such as **39** can be functionalized into nitriles which are versatile intermediates by oxidation to the N-oxide followed by reaction with DEPC and TEA or phosphorus oxychloride followed by CuCN in DMF. Details for reactions which convert **41** into **43-45** using these conditions on a similar substrate are described in reference 58 which is Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y., Tetrahedron, 1997, 53(5), 1593-1606. It should be apparent that in Schemes 12 and 13, **4b** may be replaced with any of the substrates represented by formula **4** in Scheme 4. It should also be apparent that indole **37,39, 44,** and **45** may be elaborated using appropriate chemistry described in the Schemes 5-11 herein which describe general methodology for functionalization of the azaindoles.

Scheme 13



It should be noted that 2-chloro-5-fluoro-3-nitro pyridine may be prepared by the method in example 5B of reference 59 Marfat et.al. The chemistry in Schemes 1 and 3 to provide the derivative which corresponds to general formula **5** and has a 6-aza ring and R_2=F and R_4 = Cl. In particular, reaction of 2-chloro-5-fluoro-3-nitro pyridine with 3 equivalents of vinyl Magnesium bromide using the typical conditions described herein will provide 4-fluoro-7-chloro-6-azaindole in high yield. Addition of this compound to a solution of aluminum trichloride in dichlorometane stirring at ambident temperature followed 30 minutes later

with chloromethyl or chloroethyl oxalate provides an ester. Hydrolysis with KOH as in the standard procedures herein provides an acid salt which reacts with piperazines **4** (for example 1-benzoyl piperazine) in the presence of DEPBT under the standard conditions described herein to provide the compound **5** described just above. The compound with the benzoyl piperazine is *N-(benzoyl)-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine* and is compound **5av**. The 7-chloro moiety in **5av** can be utilized by the methods of this invention to provide the desired derivatives where R_4 is substituted according to the general claim. For example, exposure of **5av** to sodium methoxide in refluxing methanol will provide the compound **5ay** in which the 6-azaindole ring contains a 4-fluoro-and 7-methoxy substituent. Alternatively, the 4-fluoro-7-chloro-6-azaindole may be reacted with sodium methoxide and then carried through the sequence as above to provide *N-(benzoyl)-N'-[(4-fluoro-7-methoxy-6-azaindol-3-yl)-oxoacetyl]-piperazine* , **5ay**. 4-fluoro-7-chloro-6-azaindole can also be reacted with CuCN/DMF as described in eq.17 to provide a 7-cyano intermediate which can be hydrolyzed to an acid as described in eq.21 Scheme 9 using HCl in MeOH at RT for 12h followed by reflux to complete the reaction. The acid can be smoothly converted to to a methly ester by adding diazomethane in ether to a stitting solution of the acid in diazometane at ambient temperature or lower. These are the standard conditions for using diazomethane which is conveniently generated as a solution in diethyl ether from Diazald® based on instructions which come with a kit from Aldrich Chemical Co. The methyl ester may be carried through the acylation using oxalyl chloride as shown in Scheme 4, followed by coupling with a piperazine (benzoyl piperazine for example) to generate the corresponding 4-fluoro-7-carbomethoxy-6-azaindole which upon addition to a solution of methylamine in water would provide **5az** which is *N-(benzoyl)-N'-[(4-fluoro-7-(N-methyl-carboxamido)-6-azaindol-3-yl)-oxoacetyl]-piperazine.* The same sequences of chemistry described above for 4-fluoro-7-chloroindole may be carried out using 7-chloro-4aza-indole and *(R)*-3-methyl-N-

benzoylpiperazine **4a** to provide **5abc** which is *(R)-N-(benzoyl)-3-methyl-N'-[(7-methoxy-4-azaindol-3-yl)-oxoacetyl]-piperazine* or **5abd** which is *(R)-N-(benzoyl)-3-methyl-N'-[(7-(N-methyl-carboxamido)-4-azaindol-3-yl)-oxoacetyl]-piperazine.* The starting 7-chloro-4-aza-indole is compound **1l** and its prepartion is described as in example in the experimental section.

It should be clear that in addition to compounds **5a–5abd** compounds **8**, **11-30**, **39**, **44**, and **45** are all compounds of formula I and are within the scope of the invention.

Detailed descriptions of many of the preparations of piperazine analogs of compounds of this invention and conditions for carrying out the general reactions described herein are described in PCT WO 00/76521 published December 21, 2000.

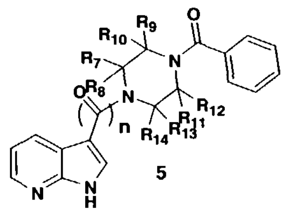
In the general routes for substituting the azaindole ring described above, each process can be applied repeatedly and combinations of these processes are permissible in order to provide azaindoles incorporating multiple substituents. The application of such processes provides additional compounds of Formula I.

Antiviral Activity

The antiviral activity of compounds was determined in HeLa CD4 CCR5 cells infected by single-round infectious HIV-1 reporter virus in the presence of compound at concentrations ≤ 10 μM. The virus infection was quantified 3 days after infection by measuring luciferase expression from integrated viral DNA in the infected cells (Chen et al, Ref. 55). The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

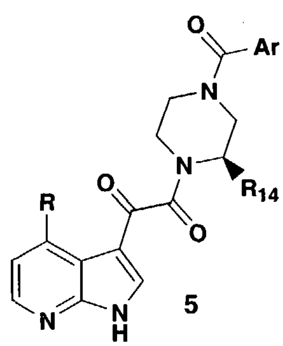
Compounds exhibiting anti-viral activity without appreciable toxicity at concentrations $\leq$ 10 μM are presented in Table I.

Table I



5

Compd #	n	R_{7-14}	Average % inhibition at or < 10 μM
5a	2	R_{7-13} = H, R_{14} = (*R*)-Me	>99%
5b	2	R_{7-8} = R_{10-14} = H, R_9 = Et	90%
5c	1	R_{7-8} = R_{10-14} = H, R_9 = Et	80%
5d	2	R_{7-14} = H	98%
5e	2	R_{7-8} = R_{10-14} = H, R_9 = Me	80%
5f	2	R_{7-13} = H, R_{14} = (*S*)-Me	80%
5g	2	R_{7-13} = H, R_{14} = Et	70%
5h	2	R_{7-12} = H, R_{13} = R_{14} = Me	80%
5i	2	R_{7-8} = R_{10-13} = H, R_9 = R_{14} = Me	89%



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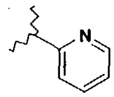
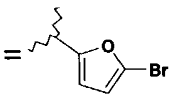
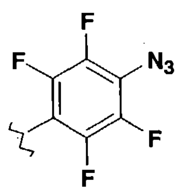
Ar = 

Compound #	R	R_{14}	Average % inhibition at or < 10 μM
5j	H	H	90%
5k	H	(*R*)-Me	>99%

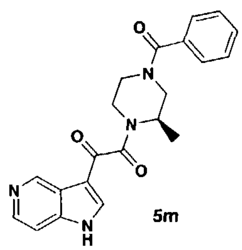
Ar = 

Compound #	R	R_{14}	Average % inhibition at or < 10 μM
5l	H	(*R*)-Me	>99%

Ar =

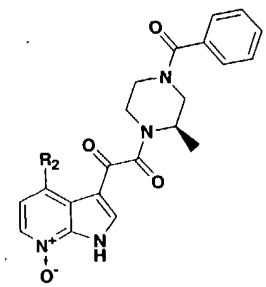


Compound #	R	R_{14}	Average % inhibition at or < 10 μM
5n	**H**	**(*R*)-Me**	**93%**

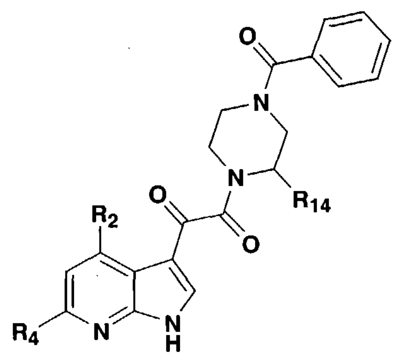


5m

Compound #	Ave.% inhibition at or < 10 μM
5m	60%

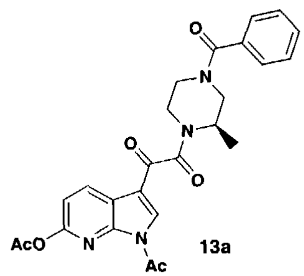


Compound #	R_2	Average % inhibition at or < 10 μM
8a	H	90%
15a	NO_2	70%
16a	OMe	>99%
16d	OEt	88%
16e	SPr	50%



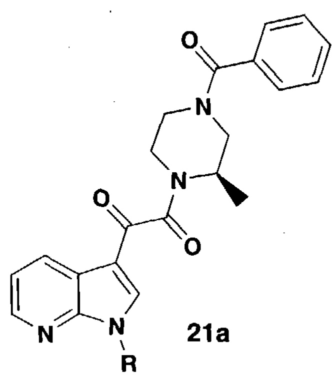
Comp #	R_2	R_4	R_{14}	Average % inhibition at or < 10 μM
9a	Cl	H	*(R)*-Me	>99%
9b	H	Cl	*(R)*-Me	>99%
10a	NO_2	F	*(R)*-Me	>99%
11a	H (when R_4=Me), Me (when R_4=H)	Me (when R_2=H), H (when R_2=Me)	*(R)*-Me	99%
11b	H (when R_4=Ph), Ph (when R_4=H)	Ph (when R_2=H), H (when R_2=Ph)	*(R)*-Me	85%
11c	H (when	Vinyl (when	*(R)*-Me	48%

	R4=vinyl), Vinyl (when R4=H)	R2=H), H (when R2=Vinyl)		
12a	H	CN	*(R)*-Me	>99%
14a	H	OH	*(R)*-Me	>99%
17a	OMe	H	*(R)*-Me	>99%
17d	OMe	H	*(S)*-Me	98%
17e	OMe	H	Me	94%
17b	OCH_2CF_3	H	*(R)*-Me	99%
17c	O-*i*-Pr	H	*(R)*-Me	>99%
18a	NO_2	H	*(R)*-Me	80%
19a	NHOH	H	*(R)*-Me	98%
20a	NH_2	H	*(R)*-Me	95%
17f	H	PrS	*(R)*-Me	>99%



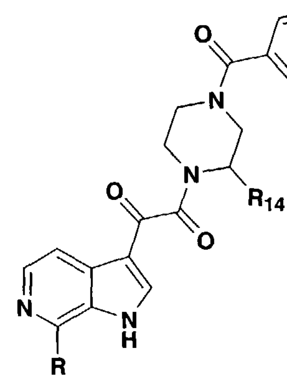
13a

Compound #	Average % inhibition at or <10 μM
13a	>99%

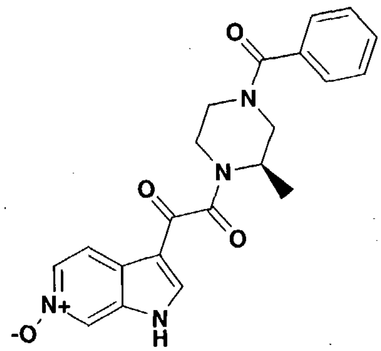


21a

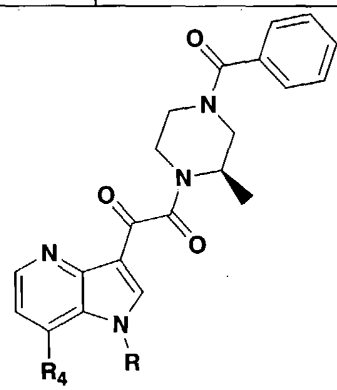
Compound #	R	Average % inhibition at or < 10 μM
21a	**Me**	**70%**
21b	**-CH2-CH=CH2**	**95%**



Compound #	R	R_{14}	Average % inhibition at or <10 □m
5p	H	*H*	40%
5r	H	*(R)*-Me	> 99%
5s	H	*(S)*-Me	56%
5q	H	Me	97%
5t	Cl	H	>99%
5u	Cl	*(R)*-Me	99%
5v	OMe	*(R)*-Me	>99%
27c	NMe_2	*(R)*-Me	63%



Compound #	Average % inhibition at or <10 □m
8b	91%



Compound #	R_4	R	Average % inhibition at or <10 □m
5w	H	H	98%
5x	Me	H	99%
5y	Cl	H	>99%
5z	OMe	Me	97%

Experimental Procedures

Biology

In Table I and hereafter, the following definitions apply.

- "μM" means micromolar;
- "ml" or "mL" means milliliter;
- "μl" means microliter;
- "mg" means milligram;
- "nM" means nanomolar
- "a" refers to percent inhibition data as representing the mean values of at least two experiments with duplicate determinations in each experiment.

The materials and experimental procedures used to obtain the results reported in Table I are described below.

Cells:

- Virus production-Human embryonic Kidney cell line, 293, propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO).

- Virus infection- Human epithelial cell line, HeLa, expressing the HIV-1 receptors CD4 and CCR5 was propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO) and supplemented with 0.2 mg/ml Geneticin (Life Technologies, Gaithersburg, MD) and 0.4 mg/ml Zeocin (Invitrogen, Carlsbad, CA).

Virus-Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al, Ref. 55). Transfections were

performed using lipofectAMINE PLUS reagent as described by the manufacturer (Life Technologies, Gaithersburg, MD).

Experiment

1. Compound was added to HeLa CD4 CCR5 cells plated in 96 well plates at a cell density of 5 X 10^4 cells per well in 100 μl Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum at a concentration of <20 μM.

2. 100 μl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 μl per well and a final compound concentration of <10 μM.

3. Samples were harvested 72 hours after infection.

4. Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit (Roche Molecular Biochemicals, Indianapolis, IN). Infected cell supernatants were removed and 50 μl of Dulbecco's Modified Eagle Medium (without phenol red) and 50 μl of luciferase assay reagent reconstituted as described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, IN) was added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac microbeta scintillation counter.

5. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for

cells infected in the absence of compound and subtracting such a determined value from 100.

Method for extrapolating % inhibition at 10μM

The data in Table 1 was obtained using the general procedures above and by the following methods. Data is not reported for all compounds since data for all the compounds is reported by the alternate method in Table 2. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100. For compounds tested at concentrations less than 10 μM, the percent inhibition at 10 μM was determined by extrapolation using the XLfit curve fitting feature of the Microsoft Excel spreadsheet software. Curves were obtained from 10 data points (% inhibition determined at 10 concentrations of compound) by using a four parameter logistic model (XLfit model 205: $y = A + ((B-A)/(1+((C/x)^D)))$, where, A = minimum y, B = maximum y, C = $\log EC_{50}$, D = slope factor, and x and y are known data values. Extrapolations were performed with the A and B parameters unlocked.

Biological Data Expressed as an EC_{50}

Table 2 presents the data for the compounds grouped based on their EC_{50} which provides an additional method for comparing the antiviral potency of the compounds of this invention. These values were calculated by the following method. The effective concentration for fifty percent inhibition (EC50) was calculated with the Microsoft Excel XLfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four paramenter logistic model (model 205).

Table 2. Biological Data Expressed as EC_{50}s

Compounds* with EC_{50}s	**Compounds with EC_{50}s >1 μM but <5μM**	**Compounds with EC50 < 1 μM**
> 0.4 μM: 5ac. >0.5 μM: 5m,5p, 5s, 5ab, 5ad, 5ae, 16b, 16c, 16h, 17f, 17g, 17h. >5 μM: 5af, 5ag, 5ah, 8e, 11c, 16e, 17g,	**5h, 11b, 18a,**	**5a, 5b, 5c, 5d, 5e, 5f, 5g, 5i, 5j, 5k, 5l, 5n, 5q, 5r, 5t, 5u, 5v, 5w, 5x, 5y, 5z, 5ai, 5ak, 5an, 5ao,5ap, 8a, 8b, 9a, 9b, 10a, 11a,12a, 13a, 15a, 16a, 16d, 17a, 17b, 17c, 17d, 17e, 19a, 20a, 21a, 21b, 27c, 39**

*Some of these compounds were tested at a concentration lower than their EC_{50} but showed some ability to cause inhibition and thus should be evaluated at a higher concentration to determine the exact EC_{50}.
An approximate attempt to exclude compounds which did not show some potential for inhibition (those which might have an EC50 > 100uM) was made.

Chemistry

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS Method (i.e., compound identification)

Column A: YMC ODS-A S7 3.0x50 mm column

Column B: PHX-LUNA C18 4.6x30 mm Column

Gradient: 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B

Gradient time: 2 minutes

Hold time 1 minute

Flow rate: 5 ml/min

Detector Wavelength: 220 nm

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

Compounds purified by preparative HPLC were diluted in methanol (1.2 ml) and purified using the following methods on a Shimadzu LC-10A automated preparative HPLC system.

Preparative HPLC Method (i.e., compound purification)

Purification Method: Initial gradient (30% B, 70% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

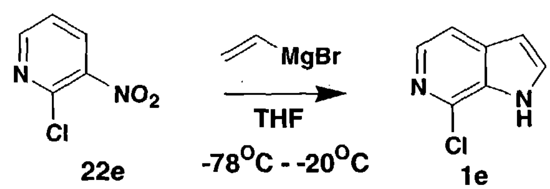
Column: YMC C18 S5 20x100 mm column

Detector Wavelength: 220 nm

Typical Procedures and Characterization of Selected Examples

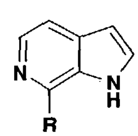
Typical Procedure for the Preparation of Compounds in Scheme 1

1) Preparation of Azaindole 1



Preparation of azaindole, Method A: Preparation of 7-Chloro-6-azaindole **1e**: 2-Chloro-3-nitropyridine **22e** (5.0 g) was dissolved in dry THF (200 ml). After the solution was cooled down to -78°C, an excess of vinyl magnesium bromide (1.0 M in THF, 100 ml) was added. Then, the reaction was left at -20°C for eight hours before quenched with 20% NH_4Cl (150 ml). The aqueous phase was extracted with EtOAc (3 x 150 ml). The combined organic layer was dried over $MgSO_4$. After filtration and concentration, the crude product was purified by silica gel column chromatography to afford 1.5 g of 7-chloro-6-azaindole **1e** in 31% yield.

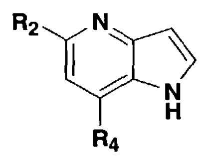
Summarized below is the characterization of compounds **1** with the following structures:



Compound 1e, R = Cl, 7-Chloro-6-azaindole: ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, 1H, J = 7.95 Hz), 7.76 (m, 2H), 6.61 (d, 1H, J = 5.45 Hz). MS m/z: $(M+H)^+$ calcd for $C_7H_6ClN_2$: 153.02; found 152.93. HPLC retention time: 0.51 minutes (column A).

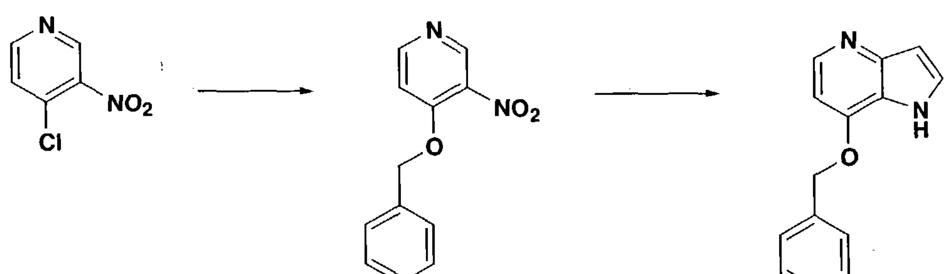
Compound 1f, R = OMe, 7-Methoxy-6-azaindole: MS m/z: $(M+H)^+$ calcd for $C_8H_9N_2O$: 149.07; found 149.00. HPLC retention time: 0.42 minutes (column A).

Characterization of compounds **1** with the following substructure prepared by the method above:



Compound **1g**, R_2 = H, R_4 = Me, 7-Methyl-4-azaindole: MS m/z: $(M+H)^+$ calcd for $C_8H_9N_2$: 133.08; found 133.01. HPLC retention time: 0.34 minutes (column A).

Compound **1ak**, R_2 = Cl, R_4 = Me, 5-Chloro-7-methyl-4-azaindole: MS m/z: $(M+H)^+$ calcd for $C_8H_8ClN_2$: 167.04; found 166.99. HPLC retention time: 1.22 minutes (column B).



Preparation of azaindole, Method A: Preparation of 7-Benzyloxy-4-

azaindole **1j**: To a solution of benzyl alcohol (16.6 g) in 200 ml of DMF was added NaH (4.8 g) slowly. The mixture was stirring at room temperature for 2 hours to afford sodium benzoxide, which was transferred into a solution of 4-chloro-3-nitropyridine hydrochloride **22j** (20 g) in DMF (100 ml). The resulting mixture was kept stirring for 10 hours before quenched with water. After DMF was removed under vaccum, the crude product was suspended in water and extracted with EtOAc (3 x 250ml). The organic phase was dried over $MgSO_4$ and concentrated to give a residue, which was purified via recrystallization to afford 6.1 g of 4-benzoxy-3-nitropyridine **22j**.

Characterization of compound **22j**:

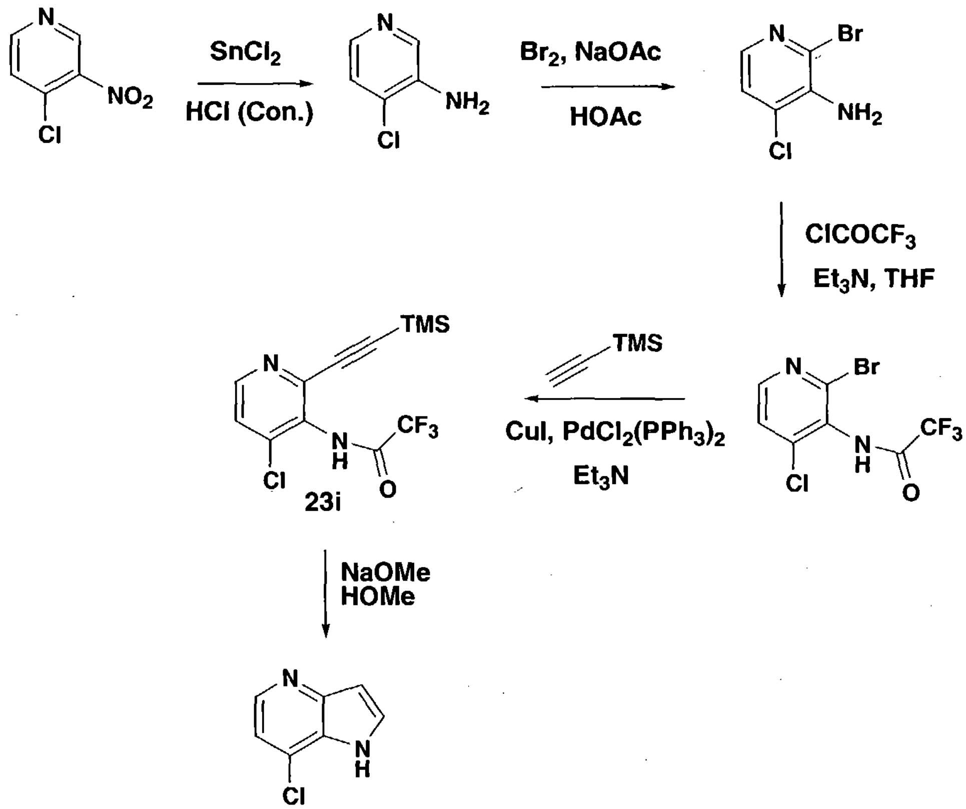
4-benzyloxy-3-nitropyridine: MS *m*/z: $(M+H)^+$ calcd for $C_{12}H_{11}N_2O_3$: 231.08; found 231.06. HPLC retention time: 1.46 minutes (column A).

Preparation of compound **1j**, 7-benzoxy-4-azaindole: The general procedure and conditions described for the Bartoli-type reaction used to prepare **1e** were followed.

Characterization of compound **1j**:

Compound **1j**, 7-benzyloxy-4-azaindole: ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (b, 1H), 8.34 (d, 1H, J = 5.35 Hz), 7.40 (m, 6H), 6.72 (d, 1H, J = 3.25 Hz), 6.67 (d, 1H, J = 5.45 Hz), 5.35 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 147.9, 145.2, 135.8, 128.8, 128.6, 127.9, 126.3, 119.6, 103.9, 99.6, 70.2. MS *m*/z: $(M+H)^+$ calcd for $C_{14}H_{13}N_2O$: 225.10; found 225.03. HPLC retention time: 1.11 minutes (column A).

Preparation of azaindole, Typical example for Method B: Preparation of 7-chloro-4-azaindole **1i**:



1i

An excess of $SnCl_2$ (25 g) was cautiously added into a solution of 4-chloro-3-nitropyridine hydrochloride (5 g) in concentrated HCl and the reaction was stirred for 12 hours. Concentration under pressure provided a mixture, which was neutralized with 2N NaOH to pH 6-7. The aqueous phase was extracted with EtOAc (5 x 100 ml). The organic layers were then combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a crude product (2.2 g), which was 4-chloro-3-nitropyridine which was pure enough for direct use in further reactions.

7g of the crude product from the previous step was dissolved in 200 ml of TFA. Then, 10.7 g of NBS was added into the mixed solution cautiously. After 8 hours, solvent was removed under vacuum. The residue was dissolved in 2N NaOH (200 ml) and aqueous layer was

extracted with EtOAc (3 x 200 ml). The combined organic layer was dried over $MgSO_4$ and concentrated to provide a crude product with was purified *via* recrystallization in hexane to afford 5 g of 3-amino-2-bromo-4-chloropyridine .

Characterization of 3-amino-2-bromo-4-chloropyridine:
MS *m/z*: $(M+H)^+$ calcd for $C_5H_5BrClN_2$: 206.93; found 206.86. HPLC retention time: 1.32 minutes (column B).

To a solution of 3-amino-2-bromo-4-chloropyridine in 250 ml of ether was added 8.4 g of trifluoroacetic anhydride at $0^{O}C$. 5.3 g of Na_2CO_3 was added 10 minutes later, and the reaction mixture was stirred at room temperature for 10 hours before the reaction was quenched with water (100 ml). The aqueous phase was extracted with EtOAc (3 x 150 ml). The combined organic layer was dried over $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography to afford 3.7 g of compound **23i**.

Characterization of compound **23i**:

2-Bromo-4-chloro-3-trifluoroacetaminopyridine: MS *m/z*: $(M+H)^+$ calcd for $C_7H_4BrClF_3N_2O$: 302.90; found 302.91. HPLC retention time: 1.48 minutes (column B).

A mixture of compound **23i** (0.9 g), trimethylsilylacetylene (0.49 g), Pd $Cl_2(PPh_3)_2$ (0.1 g) and CuI (0.05g) in Et_3N (1.5 ml) was heated to $100^{O}C$ in sealed tube for 10 hours. Then, solvent was removed under vaccum. The residue was partitioned between water (10 ml) and EtOAc (10 ml). Aqueous phase was extracted with EtOAc (2 x 10 ml). The combined organic layer was dried over $MaSO_4$ and concentrated under vaccum to provide a crude product **24i** which was used in the further reaction without purification.

Characterization of compound **24i**:

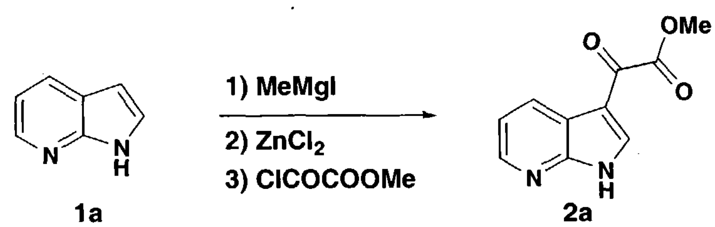
Compound **24i**, 4-Chloro-3-trifluoroacetamido-2-(trimethylsilylethynyl)pyridine: MS *m/z*: $(M+H)^+$ calcd for $C_7H_4BrClF_3N_2O$: 321.04; found 320.99. HPLC retention time: 1.79 minutes (column B).

A mixture of compound **24i** (0.28 g) and sodium ethoxide (0.30 ml) in 20 ml of ethanol was heated to reflux for 10 hours under nitrogen atmosphere. After solvent removed under vaccum, the residue was purified using Shimadzu automated preparative HPLC System to give compound **1i** (0.1 g).

Characterization of compound **1i**:

Compound **1i**, 7-Chloro-4-azaindole: ^1H NMR (500 MHz, CD_3OD) δ 8.50 (d, 1H, J = 6.20 Hz), 8.10 (d, 1H, J = 3.20 Hz), 7.71 (d, 1H, J = 6.30 Hz), 6.91 (d, 1H, J = 3.25 Hz). MS *m/z*: $(M+H)^+$ calcd for $C_7H_6ClN_2$: 153.02; found 152.90. HPLC retention time: 0.45 minutes (column A).

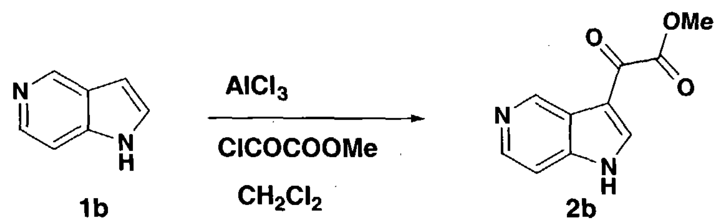
1) ***Preparation of azaindole 3-glyoxylmethyl ester 2***



Acylation of azaindole, method A: Preparation of Methyl (7-azaindol-3-yl)-oxoacetate ***2a***: To a solution of 7-azaindole **1a** (20.0 g, 0.169 mol) in dry CH_2Cl_2 (1000 ml), 62.1 ml of MeMgI (3.0M in Et_2O, 0.186 mol) was added at room temperature. The resulting mixture was stirred at room temperature for 1 hour before $ZnCl_2$ (27.7 g, 0.203 mol) was added. One hour later, methyl chlorooxoacetate (24.9 g, 0.203 mol)

was injected into the solution dropwise. Then the reaction was stirred for 8 hours before being quenched with methanol.

After all solvents were evaporated, the residue was partitioned between ethyl acetate (500 ml) and H_2O (300 ml). The aqueous phase was neutralized with saturated Na_2CO_3 to pH 6-6.5, and extracted with EtOAc (3 x 500 ml). The organic layers were then combined, washed with 0.1N HCl (3 x 200 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a crude product **2a** (14.3 g, 41.5%), which was pure enough for the further reactions.

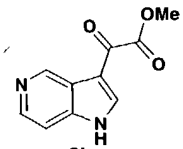


*Acylation of azaindole, method B: Preparation of Methyl (5-azaindol-3-yl)-oxoacetate **2b***: 5-Azaindole **1b** (0.5 g, 4.2 mmol) was added to a suspension of $AlCl_3$ (2.8 g, 21.0 mmol) in CH_2Cl_2 (100 ml). Stirring was continued at room temperature for 1 hour before methyl chlorooxoacetate (2.5 g, 21.0 mmol) was added dropwise. The reaction was stirred for 8 hours. After 20 ml of MeOH was added cautiously to quench the reaction, solvents were removed under vaccum. The solid residue was purified by silica gel column chromatography (EtOAc/MeOH = 10 : 1) to afford 0.6 g (70%) of the acylated product **2b**.

Characterization of compounds **2**:

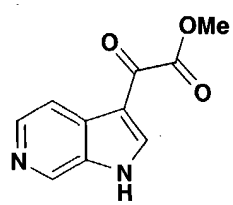
Compound **2a**, *Methyl (7-azaindol-3-yl)-oxoacetate*: ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.60 (s, 1H), 8.47 (d, 1H, J = 7.86 Hz), 8.40 (d, 1H, J = 4.71 Hz), 7.34 (dd, 1H, J = 7.86, 4.77 Hz), 3.99 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 178.7, 163.3, 149.0, 145.1, 138.8, 129.7, 119.0, 118.0,

111.2, 52.7. MS m/z: $(M+H)^+$ calcd for $C_{10}H_9N_2O_3$: 205.06; found 205.04. HPLC retention time: 0.94 minutes (column A).



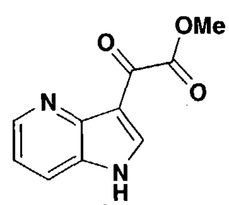
2b

Compound **2b**, *Methyl (5-azaindol-3-yl)-oxoacetate*: ^1H NMR (500 MHz, CD_3OD) δ 9.61 (s, 1H), 9.02 (s, 1H), 8.59 (d, 1H, J = 6.63 Hz), 8.15 (d, 1H, J = 6.60 Hz), 4.00 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 178.9, 163.0, 145.6, 144.2, 138.3, 135.0, 124.7, 116.3, 112.1, 53.8. MS m/z: $(M+H)^+$ calcd for $C_{10}H_9N_2O_3$: 205.06; found 205.04. HPLC retention time: 0.32 minutes (column A).



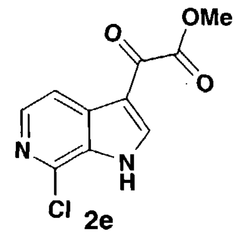
2c

Compound **2c**, *Methyl (6-azaindol-3-yl)-oxoacetate*: MS m/z: $(M+H)^+$ calcd for $C_{10}H_9N_2O_3$: 205.06; found 205.14. HPLC retention time: 0.61 minutes (column A).



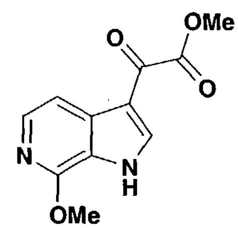
2d

Compound **2d**, *Methyl (4-azaindol-3-yl)-oxoacetate*: MS m/z: $(M+H)^+$ calcd for $C_{10}H_9N_2O_3$: 205.06; found 204.99. HPLC retention time: 0.34 minutes (column A).



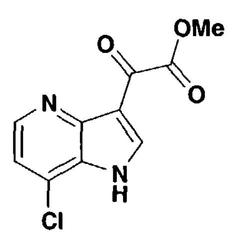
2e

Compound **2e**, *Methyl (7-chloro-6-azaindol-3-yl)-oxoacetate*: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (s, 1H), 8.17 (d, 1H, J = 5.35 Hz), 8.05 (d, 1H, J = 5.30 Hz), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 178.4, 162.7, 141.3, 140.9, 134.6, 133.0, 130.1, 115.4, 113.0, 52.8. MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.97. HPLC retention time: 1.18 minutes (column A).



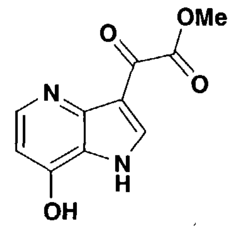
2f

Compound **2f**, *Methyl (7-methoxy-6-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ calcd for $C_{11}H_{11}N_2O_4$: 235.07; found 234.95. HPLC retention time: 0.95 minutes (column A).



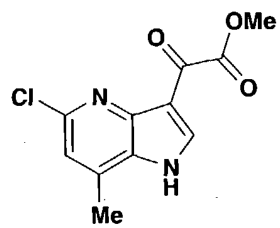
2h

Compound **2h**, *Methyl (7-chloro-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.97. HPLC retention time: 0.60 minutes (column A).

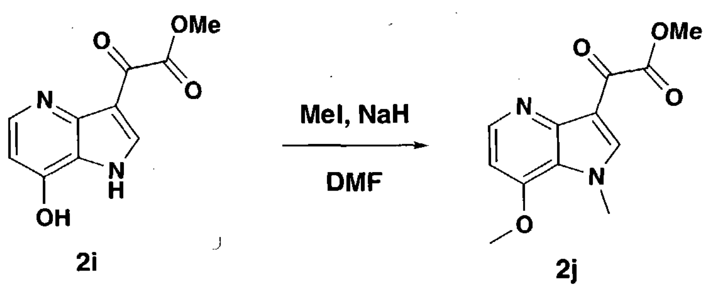


2i

Compound **2i**, *Methyl (7-hydroxyl-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_9N_2O_4$: 221.06; found 220.96. HPLC retention time: 0.76 minutes (column A).



Compound **2ak**, *Methyl (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ calcd for $C_{11}H_{10}ClN_2O_3$: 253.04; found 252.97. HPLC retention time: 1.48 minutes (column B).

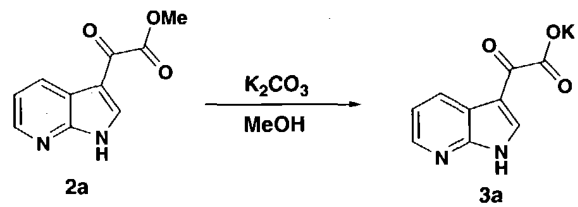


Preparation of compound 2j, Methyl (7-methoxyl-1-methyl-4-azaindol-3-yl)-oxoacetate: To a solution of compound **2i** (27 mg) in 10 ml of dry DMF was added 4.4 mg of NaH. After 1 hour, 26 mg of MeI was added and the mixture was stirred at room temperature for 10 hours. DMF was then removed under vaccum to provide a crude product **2j** which was used in the further reaction without purification.

Characterization of compounds **2j**:

Compound **2j**, *Methyl (7-methoxy-1-methyl-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ calcd for $C_{12}H_{13}N_2O_4$: 249.09; found 249.33. HPLC retention time: 0.91 minutes (column A).

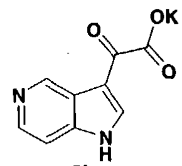
2) Preparation of potassium azaindole 3-glyoxylate 3



*Preparation of Potassium (7-azaindol-3-yl)-oxoacetate **3a***: Compound **2a** (43 g, 0.21 mol) and K_2CO_3 (56.9g, 0.41 mol) were dissolved in MeOH (200 ml) and H_2O (200 ml). After 8 hours, product **3a** precipitated out from the solution. Filtration afforded 43 g of compound **3a** as a white solid in 90.4% yield.

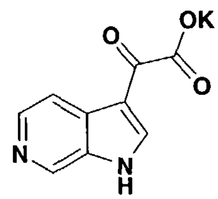
Characterization of compounds **3**:

Compound **3a**, *Potassium (7-azaindol-3-yl)-oxoacetate*: ^1H NMR (300 MHz, DMSO-d_6) δ 8.42 (d, 1H, J = 7.86 Hz), 8.26 (d, 1H, J = 4.71 Hz), 8.14 (s, 1H), 7.18 (dd, 1H, J = 7.86, 4.71Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 148.9, 143.6, 135.1, 129.3, 118.2, 117.5, 112.9. MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3a** (**3a**–K+H) calcd for $C_9H_7N_2O_3$: 191.05; found 190.97. HPLC retention time: 0.48 minutes (column A).



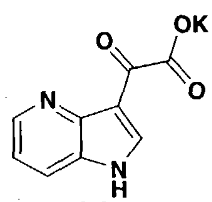
3b

Compound **3b**, *Potassium (5-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3b** (**3b**–K+H) calcd for $C_9H_7N_2O_3$: 191.05; found 191.02. HPLC retention time: 0.13 minutes (column A).



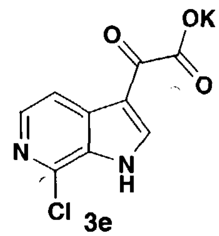
3c

Compound **3c**, *Potassium (6-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3c** (**3c**–K+H) calcd for $C_9H_7N_2O_3$: 191.05; found 190.99. HPLC retention time: 0.23 minutes (column A).



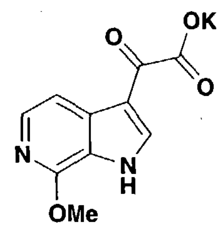
3d

Compound **3d**, *Potassium (4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3d** (**3d**–K+H) calcd for $C_9H_7N_2O_3$: 191.05; found 190.87. HPLC retention time: 0.19 minutes (column A).



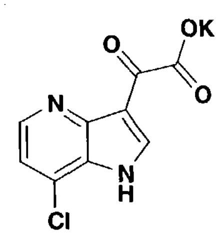
3e

Compound **3e**, *Potassium (7-chloro-6-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3e** ($\mathbf{3e}$–K+H)$^+$ calcd for $C_9H_6ClN_2O_3$: 225.01; found 224.99. HPLC retention time: 0.93 minutes (column A).



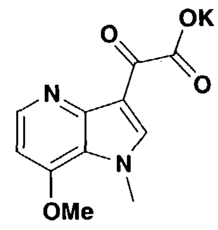
3f

Compound **3f**, *Potassium (7-methoxy-6-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3f** ($\mathbf{3f}$–K+H)$^+$ calcd for $C_{10}H_9N_2O_4$: 221.06; found 220.97. HPLC retention time: 0.45 minutes (column A).



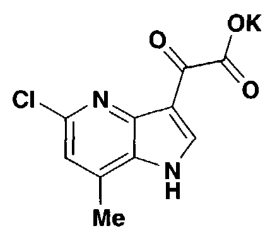
3h

Compound **3h**, *Potassium (7-chloro-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3h** ($\mathbf{3h}$–K+H)$^+$ calcd for $C_9H_6ClN_2O_3$: 225.01; found 225.27. HPLC retention time: 0.33 minutes (column A).



3j

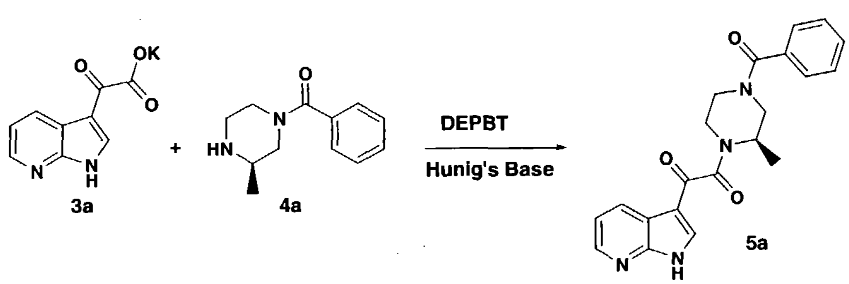
Compound **3j**, Potassium (7-methoxyl-1-methyl-4-azaindol-3-yl)-oxoacetate: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3j** (**3j**–K+H)$^+$ calcd for $C_{11}H_{11}N_2O_4$: 235.07; found 235.01. HPLC retention time: 0.36 minutes (column A).



Compound **3ak**, *Potassium (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate*: MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3ak** (**3ak**–K+H)$^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.94. HPLC retention time: 1.24 minutes (column B).

1) Preparation of azaindole piperazine diamide 5

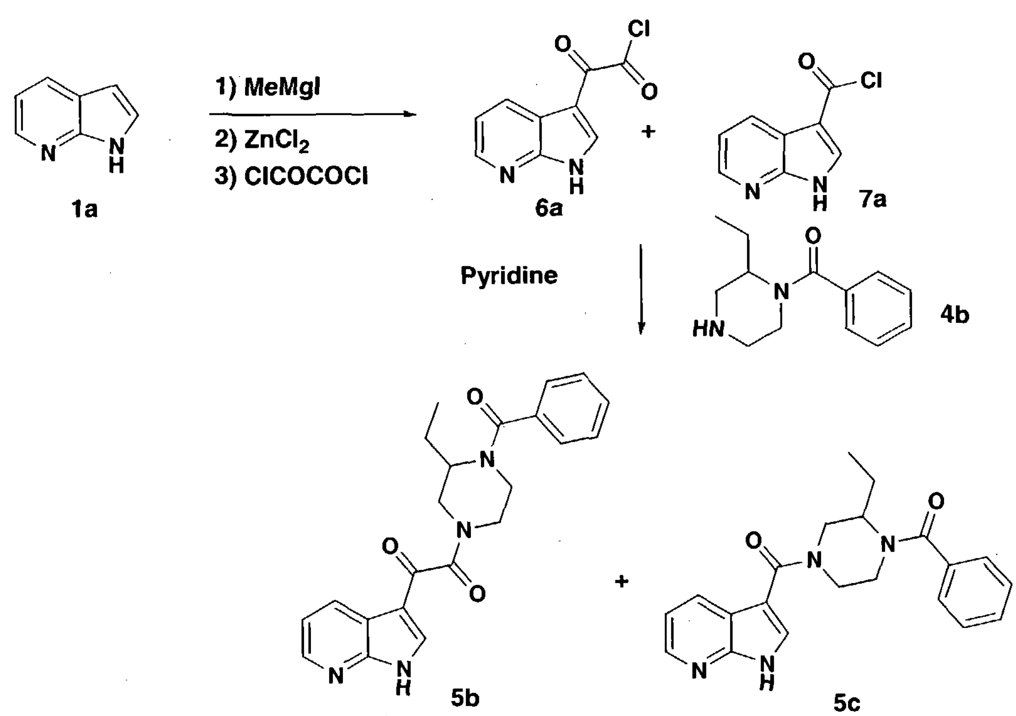
Typical Procedure for the Preparation of Compounds in Scheme 3



Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine ***5a***: Potassium 7-azaindole 3-glyoxylate **3a** (25.4 g, 0.111 mol), *(R)*-3-methyl-N-benzoylpiperazine **4a** (22.7 g, 0.111 mol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (33.3 g, 0.111 mol) and Hunig's Base (28.6 g, 0.222 mol) were combined in 500 ml of DMF. The mixture was stirred at room temperature for 8 hours.

DMF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate (2000 ml) and 5% Na_2CO_3 *aqueous solution (2 x 400 ml). The aqueous layer was extracted with* ethyl acetate (3 x 300 ml). The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by silica gel column chromatography with EtOAc/MeOH (50:1) to give 33 g of product **5a** in 81% yield.

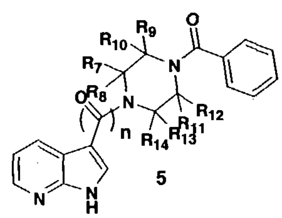
Typical Procedure for the Preparation of Compounds in Scheme 4



Preparation of N-(benzoyl)-2-ethyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine ***5b*** *and N-(benzoyl)-2-ethyl-N'-[(7-azaindol-3-yl)-carbonyl]-piperazine* ***5c***: To a solution of 7-azaindole **1a** (1.0 g, 8.5 mmol) in dry diethyl ether (20 ml), 3.1 ml of MeMgI (3.0M in Et_2O, 9.3 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for 1 hour before $ZnCl_2$ (1M in ether, 10.2 ml, 10.2 mmol) was added. One hour later, oxalyl chloride (10.7 g, 85 mmol) was injected into the solution cautiously. After the reaction was stirred for 8 hours, solvent and excess oxayl chloride were removed under vaccum to give a residue containing a mixture of **6a** and **7a**.

After the residue was dissolved in dry CH_3CN (8 ml), mono-benzoylated piperazine **4b** (0.25 g, 1.15 mmol) and pyridine (1 g, 12.7 mmol) were added into the solution subsequently. 1 hour later, solvents were removed and residue was purified using Shimadzu automated preparative HPLC System to give compound **5b** (20 mg, 0.6%) and compound **5c** (16 mg, 0.5%).

Characterization of compounds **5** with the following sub-structure:



5

Compound **5a**, n = 2, $R_{7\text{-}13}$ = H, R_{14} = (*R*)-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, CD_3OD) δ 8.57 (d, 1H, J = 5.97 Hz), 8.38 (d, 1H, J = 4.20 Hz), 8.27 (m, 1H), 7.47 (s, 5H), 7.35 (t, 1H, J = 5.13 Hz), 4.75-2.87 (m, 7H), 1.31 (b, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 185.6, 172.0, 166.3, 148.9, 144.6, 137.0, 134.8, 130.2, 129.9, 128.4, 126.6, 118.6, 118.0, 112.2, 61.3, 50.3,

45.1, 35.5, 14.9, 13.7. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$: 377.16; found 377.18. HPLC retention time: 1.21 minutes (column A).

Compound **5ai**, n = 2, R_{7-13} = H, R_{14} = Me, *N-(benzoyl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$: 377.16; found 377.05.

Compound **5b**, n = 2, R_{7-8} = R_{10-14} = H, R_9 = Et, *N-(benzoyl)-2-ethyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 8.40 (s, 1H), 8.25 (m, 1H), 7.42 (m, 6H), 4.70-2.90 (m, 7H), 1.80-0.60 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ 186.8, 174.2, 168.3, 149.6, 145.4, 138.8, 136.9, 132.6, 131.3, 130.0, 128.0, 120.2, 117.7, 114.1, 58.4, 52.2, 47.5, 44.8, 23.0, 10.9, 10.7. MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_3$: 391.18; found 391.22. HPLC retention time: 1.35 minutes (column A).

Compound **5c**, n = 1, R_{7-8} = R_{10-14} = H, R_9 = Et, *N-(benzoyl)-2-ethyl-N'-[(7-azaindol-3-yl)-carbonyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.33(m, 2H), 7.87 (s, 1H), 7.47 (m, 5H), 7.33 (m, 1H), 4.74-2.90 (m, 7H), 1.78-0.75 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.0, 164.2, 162.8, 147.0, 142.8, 136.9, 133.1, 132.8, 131.3, 130.4, 130.0, 128.0, 118.4, 110.3, 57.0, 53.4, 46.7, 24.0, 10.7. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{23}N_4O_2$: 363.18; found 363.22. HPLC retention time: 1.14 minutes (column A).

Compound **5d**, n = 2, R_{7-14} = H, *N-(benzoyl)-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.62 (s, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 7.46 (s, 5H), 7.29 (m, 1H), 3.97-3.31 (m, 8H). MS *m*/z: $(M+H)^+$ calcd for $C_{20}H_{19}N_4O_3$: 363.15; found 363.24. HPLC retention time: 1.18 minutes (column A).

Compound **5e**, n = 2, R_{7-8} = R_{10-14} = H, R_9 = Me, *N-(benzoyl)-2-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.64 (s, 1H), 8.51 (s, 1H), 8.28 (m, 1H), 7.42 (m, 6H), 4.48-2.90 (m, 7H), 1.26 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) □δ 185.3, 171.4, 166.8, 164.0, 147.9, 143.6, 137.3, 135.3, 131.2, 129.8, 128.4, 126.2, 118.6, 112.4, 49.4, 45.9, 45.6, 45.1, 40.8, 40.4, 14.1. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$: 377.16; found 377.21. HPLC retention time: 1.26 minutes (column A).

Compound **5f**, n = 2, R_{7-13} = H, R_{14} = (*S*)-Me, *(S)-N-(benzoyl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.64 (s, 1H), 8.39 (s, 1H), 8.26 (m, 1H), 7.44 (m, 6H), 4.71-3.79 (m, 7H), 1.26 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.5, 171.9, 166.0, 158.4, 147.6, 143.5, 137.2, 134.8, 131.3, 129.8, 128.3, 126.6, 118.6, 112.4, 50.3, 45.1, 41.2, 40.3, 14.9, 13.7. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$: 377.16; found 377.21. HPLC retention time: 1.25 minutes (column A).

Compound **5g**, n = 2, R_{7-13} = H, R_{14} = Et, *N-(benzoyl)-3-ethyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.65 (b, 1H), 8.40 (s, 1H), 8.27 (m, 1H), 7.46 (m, 6H), 4.73-3.00 (m, 7H), 1.80-0.58 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ 187.1, 173.0, 168.0, 149.2, 145.0, 138.8, 136.4, 133.0, 131.4, 129.9, 128.2, 120.2, 114.1, 57.5, 46.0, 43.0, 37.5, 23.0, 10.7. MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_3$: 391.18; found 391.20. HPLC retention time: 1.33 minutes (column A).

Compound **5h**, n = 2, R_{7-12} = H, R_{13} = R_{14} = Me, *N-(benzoyl)-3,3-dimethyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_3$: 391.18; found 390.98. HPLC retention time: 1.22 minutes (column A).

Compound **5i**, n = 2, R_{7-8} = R_{10-13} = H, R_9 = R_{14} = Me, *trans-N-(benzoyl)-2,5-dimethyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^1H NMR (500 MHz, CD_3OD) δ 8.58 (m, 1H), 8.37 (d, 1H, J = 15.7 Hz), 8.25 (m, 1H), 7.77 (m, 1H), 7.46 (m, 5H), 5.09-3.16 (m, 6H), 1.30 (m, 6H). MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_3$: 391.18; found 391.11. HPLC retention time: 1.22 minutes (column A).

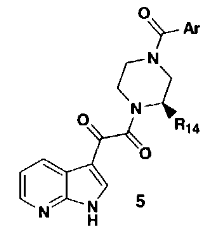
Compound **5ab**, n = 2, R_{7-9} = R_{10-13} = H, R_{14} = i-Pr, *N-(benzoyl)-3-iso-Propyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_3$: 405.19; found 405.22. HPLC retention time: 1.52 minutes (column A).

Compound **5ac**, n = 2, R_{7-8} = R_{10-14} = H, R_9 = i-Pr, *N-(benzoyl)-2-iso-Propyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_3$: 405.19; found 405.25. HPLC retention time: 1.53 minutes (column A).

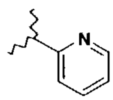
Compound **5ad**, n = 1, R_{7-8} = R_{10-14} = H, R_9 = i-Pr, *N-(benzoyl)-2-iso-Propyl-N'-[(7-azaindol-3-yl)-carbonyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{25}N_4O_2$: 377.20; found 377.23. HPLC retention time: 1.34 minutes (column A).

Compound **5ae**, n = 2, R_{7-8} = R_{10-14} = H, R_9 = Pentyl, *trans-N-(benzoyl)-2-Pentyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{25}H_{29}N_4O_3$: 433.22; found 433.42. HPLC retention time: 1.74 minutes (column A).

Characterization of compounds **5** with the following sub-structure:

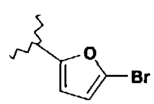


5

When Ar = 

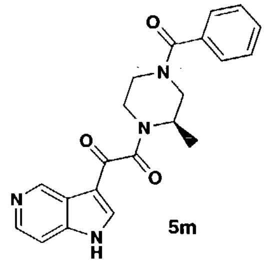
Compound **5j**, R_{14} = H, *N-(pyridin-2-yl)-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.65-7.30 (m, 8H), 4.00-3.33 (m, 8H). MS *m/z*: $(M+H)^+$ calcd for $C_{19}H_{18}N_5O_3$: 364.14; found 364.08. HPLC retention time: 0.97 minutes (column A).

Compound **5k**, R_{14} = (*R*)-Me, *(R)-N-(pyridin-2-yl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, CD_3OD) δ 8.67-7.38 (m, 8H), 4.76-3.00 (m, 7H), 1.35 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 186.0, 168.9, 166.6, 152.9, 148.5, 144.0, 138.7, 137.8, 131.8, 125.6, 124.0, 119.0, 112.9, 51.3, 50.9, 50.7, 46.7, 46.2, 45.7, 42.6, 42.0, 41.8, 40.8, 36.6, 35.7, 15.5, 14.2. MS *m/z*: $(M+H)^+$ calcd for $C_{20}H_{20}N_5O_3$: 378.16; found 378.14. HPLC retention time: 1.02 minutes (column A).

When Ar = 

Compound **5l**, R_{14} = (*R*)-Me, *(R)-N-(5-bromo-furan-2-yl)-3-methyl-N'-[(7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (d, 1H, *J* = 9.4 Hz), 8.37 (s, 1H), 8.26 (m, 1H), 7.34 (d, 1H, *J* = 10.1Hz), 7.06 (s, 1H), 6.59 (s, 1H), 4.56-3.16 (m, 7H), 1.30 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD). δ 187.2, 167.8, 161.0, 150.1, 149.8, 145.8, 138.7, 132.1, 127.0, 120.5, 120.2, 119.8, 114.8, 113.9, 51.8, 47.0, 42.0,

37.0, 16.6, 15.4. MS *m/z*: $(M+H)^+$ calcd for $C_{19}H_{18}BrN_4O_4$: 445.05; found 445.18. HPLC retention time: 1.35 minutes (column A).

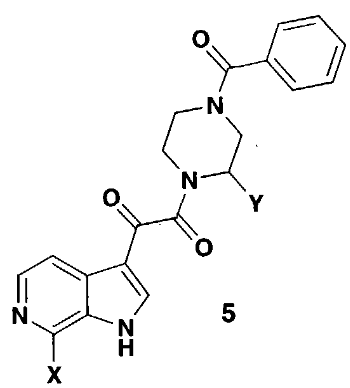


5m

Characterization of compound **5m**:

Compound **5m**, *(R)-N-(benzoyl)-3-methyl-N'-[(5-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 9.62 (b, 1H), 8.72 (m, 1H), 8.61 (d, 1H, *J* = 4.5 Hz), 8.16 (d, 1H, *J* = 5.8 Hz), 7.51 (b, 6H), 4.90-3.10 (m, 7H), 1.35 (b, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 377.16, found 377.15. HPLC retention time: 0.89 minutes (column A).

Characterization of compounds **5** with the following sub-structure:



5

Compound **5p**, X = H, Y = H, *N-(benzoyl)-N'-[(6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{20}H_{19}N_4O_3$ 363.15, found 363.09. HPLC retention time: 0.96 minutes (column A).

Compound **5q**, X = H, Y = Me, *N-(benzoyl)-3-Methyl-N'-[(6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 377.16, found 377.11. HPLC retention time: 0.99 minutes (column A).

Compound **5r**, X = H, Y = *(R)*-Me, *(R)-N-(benzoyl)-3-Methyl-N'-[(6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 377.16, found 377.10. HPLC retention time: 0.99 minutes (column A).

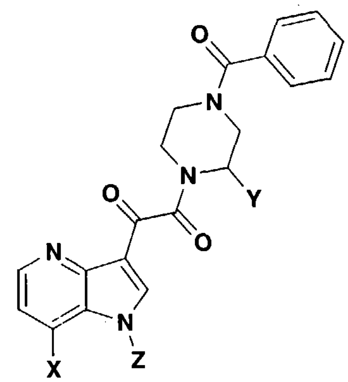
Compound **5s**, X = H, Y = *(S)*-Me, *(S)-N-(benzoyl)-3-Methyl-N'-[(6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 377.16, found 377.10. HPLC retention time: 1.00 minutes (column A).

Compound **5t**, X = Cl, Y = H, *N-(benzoyl)-N'-[(7-Chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{20}H_{18}ClN_4O_3$ 397.11, found 397.26. HPLC retention time: 1.60 minutes (column B).

Compound **5u**, X = Cl, Y = *(R)*-Me, *(R)-N-(benzoyl)-3-Methyl-N'-[(7-Chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$ 411.12, found 411.16. HPLC retention time: 1.43 minutes (column A).

Compound **5v**, X = OMe, Y = *(R)*-Me, *(R)-N-(benzoyl)-3-Methyl-N'-[(7-Methoxy-6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$ 407.17, found 407.13. HPLC retention time: 1.31 minutes (column A).

Characterization of compounds **5** with the following sub-structure:

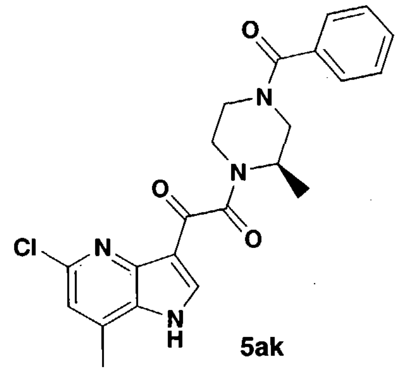


Compound **5w**, X = H, Y = *(R)*-Me, Z = H, *(R)-N-(benzoyl)-3-Methyl-N'-[(4-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 377.16, found 377.14. HPLC retention time: 0.96 minutes (column A).

Compound **5x**, X = CH_3, Y = *(R)*-Me, Z = H, *(R)-N-(benzoyl)-3-Methyl-N'-[(7-Methyl-4-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 391.18, found 391.15. HPLC retention time: 1.15 minutes (column A).

Compound **5y**, X = Cl, Y = *(R)*-Me, Z = H, *(R)-N-(benzoyl)-3-Methyl-N'-[(7-Chloro-4-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$ 411.12, found 411.04. HPLC retention time: 1.10 minutes (column A).

Compound **5z**, X = OMe, Y = *(R)*-Me, Z = Me, *(R)-N-(benzoyl)-3-Methyl-N'-[(7-Methoxy-1-methyl-4-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_4$: 421.19, found 421.05. HPLC retention time: 1.06 minutes (column A).

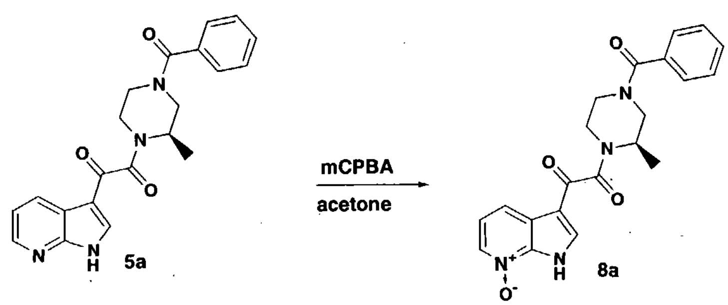


5ak

Compound **5ak**, *(R)-N-(benzoyl)-3-Methyl-N'-[(5-Chloro-7-methyl-4-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{22}ClN_4O_3$ 425.24, found 425.04. HPLC retention time: 1.72 minutes (column B).

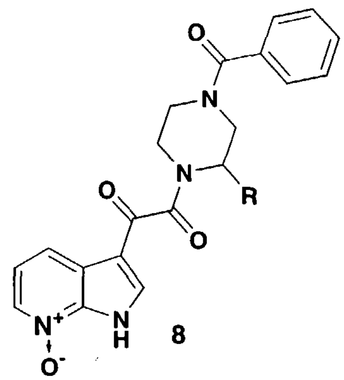
Typical Procedure for Preparation of Compounds in Scheme 5, 6 and 7

1) N-Oxide formation (equation 1, Scheme 5)



Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine ***8a***: 10 g of 7-azaindole piperazine diamide **5a** (26.6 mmol) was dissolved in 250 ml acetone. 9.17 g of mCPBA (53.1 mmol) was then added into the solution. Product **8a** precipitated out from the solution as a white solid after 8 hours and was collected via filtration. After drying under vacuum, 9.5 g of compound **8a** was obtained in 91% yield. No further purification was needed.

Characterization of compound **8** with he following sub-structure:



8

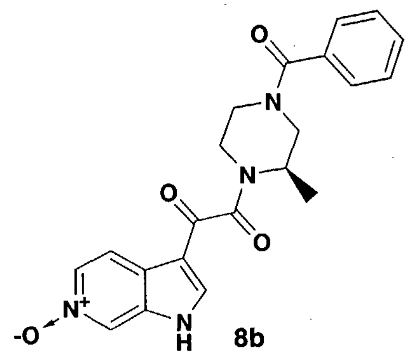
Compound **8a**, R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (d, 1H, J = 12.2 Hz), 8.26 (d, 1H, J = 10.1 Hz), 8.00 (d, 1H, J = 7.41 Hz), 7.41 (s, 5H), 7.29 (m, 1H), 4.57-2.80 (m, 7H), 1.19 (b, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 186.2, 170.0, 165.0, 139.5, 136.9, 136.7, 135.5, 133.5, 129.7, 128.5, 126.9, 121.6, 119.9, 113.6, 49.4, 44.3, 15.9, 14.8. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.16. HPLC retention time: 1.05 minutes (column A).

Compound **8e**, R = H, *N-(benzoyl)-N'-[(7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{20}H_{19}N_4O_4$: 379.14; found 379.02. HPLC retention time: 1.15 minutes (column A).

Compound **8c**, R = *(S)*-Me, *(S)-N-(benzoyl)-3-methyl-N'-[(7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.05.

Compound **8d**, R = Me, *N-(benzoyl)-3-methyl-N'-[(7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.05.

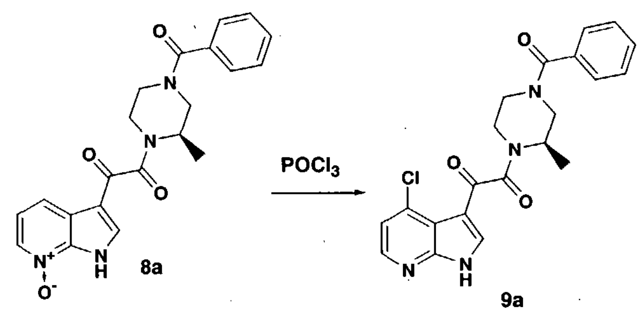
Characterization of compound **8b**:



8b

Compound **8b**, *(R)-N-(benzoyl)-3-methyl-N'-[(6-oxide-6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.08. HPLC retention time: 1.06 minutes (column A).

2) Chlorination (equation 2, Scheme 5)

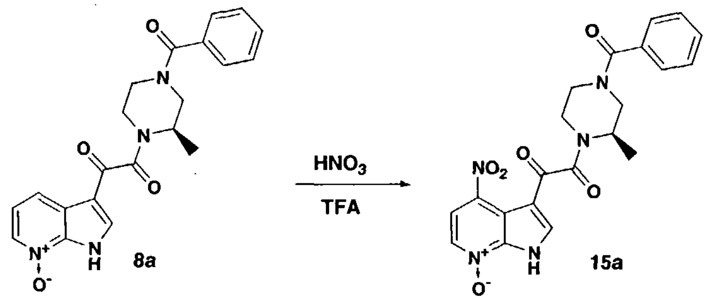


*Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-chloro-7-azaindol-3-yl)-oxoacetyl]-piperazine **9a***: 55 mg of 7-azaindole piperazine diamide *N*-Oxide (0.14 mmol) **8a** was dissolved in 5 ml of $POCl_3$. The reaction mixture was heated at 60^{O}C for 4 hours. After cooling, the mixture was poured into ice cooled saturated $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc (3 x 50 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified using a Shimadzu automated preparative HPLC System to give compound **9a** (15 mg, 26%).

Characterization of compound **9a**:

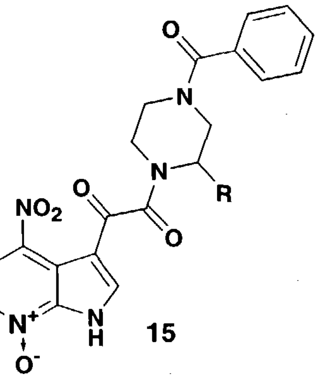
Compound **9a**, *(R)-N-(benzoyl)-3-methyl-N'-[(4-chloro-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.27 (b, 1H), 8.46 (m, 2H), 7.43 (m, 6H), 5.00-2.80 (m, 7H), 1.23 (b, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$: 411.12; found 411.09. HPLC retention time: 1.32 minutes (column A).

3) *Nitration of N-Oxide (equation 10, Scheme 6)*



*Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-nitro-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine **15a***: *N*-oxide **8a** (10.8 g, 27.6 mmol) was dissolved in 200 ml of trifluoroacetic acid and 20 ml of fuming nitric acid. The reaction mixture was stirred for 8 hours and quenched with methanol. After filtration, the filtrate was concentrated under vacuum to give crude product **15a** as a brown solid, which was carried to the next step without further purification. A small amount of crude product was purified using a Shimadzu automated preparative HPLC System to give compound 3 mg of compound **15a**.

Characterization of compound **15** with the following sub-structure:



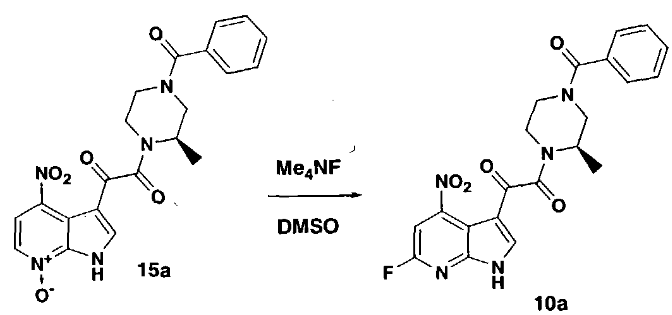
15

Compound **15a**, R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-nitro-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}N_5O_6$: 438.14; found 438.07. HPLC retention time: 1.18 minutes (column A).

Compound **15b**, R = *(S)*-Me, *(S)-N-(benzoyl)-3-methyl-N'-[(4-nitro-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}N_5O_6$: 438.14; found 438.02. HPLC retention time: 1.18 minutes (column A).

Compound **15c**, R = Me, *N-(benzoyl)-3-methyl-N'-[(4-nitro-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}N_5O_6$: 438.14; found 438.02. HPLC retention time: 1.18 minutes (column A).

4) Fluorination (equation 5, Scheme 3)

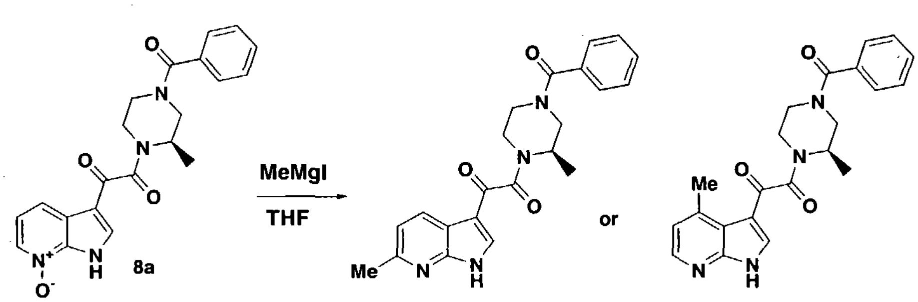


Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-nitro-6-fluoro-7-azaindol-3-yl)-oxoacetyl]-piperazine ***10a***: 20 mg of crude 4-nitro-7-azaindole piperazine diamide *N*-oxide **15a** and an excess of Me_4NF (300 mg) were dissolved in 5 ml of DMSO-d_6. The reaction mixture was heated at 100^{O}C for 8 hours. After cooling, DMSO-d_6 was removed by blowing nitrogen. The residue was partitioned between ethyl acetate (10 ml) and 2N NaOH solution (10 ml). The aqueous phase was extracted with EtOAc (2 x 10 ml). The organic layers were combined and concentrated under vacuum to give a residue, which was further purified using a Shimadzu automated preparative HPLC System to give compound of **10a** (8.3 mg).

Characterization of compound **10a**:

Compound **10a**: *(R)-N-(benzoyl)-3-methyl-N'-[(4-nitro-6-fluoro-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.44 (d, 1H, J = 8.24 Hz), 7.47 (s, 6H), 4.80-3.00 (m, 7H), 1.29 (b, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{19}FN_5O_5$: 440.14; found 440.14. HPLC retention time: 1.40 minutes (column B).

5) Alkylation and Arylation (equation 4, Scheme 5)

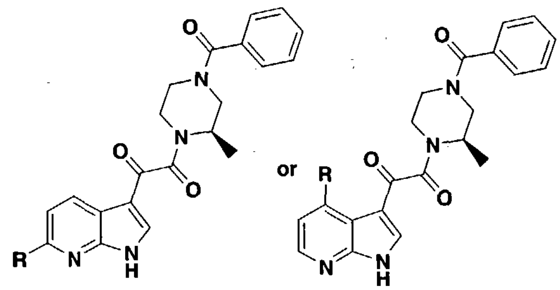


11a

Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4 or 6)-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine ***11a:*** An excess of MeMgI (3M in THF, 0.21 ml, 0.63 mmol) was added into a solution of 7-azaindole

piperazine diamide *N*-oxide **8a** (25 mg, 0.064 mmol). The reaction mixture was stirred at room temperature and then quenched with methanol. The solvents were removed under vacuum, the residue was diluted with methanol and purified using a Shimadzu automated preparative HPLC System to give compound **11a** (6.7 mg, 27%).

Characterization of compounds **11** with the following sub-structure:



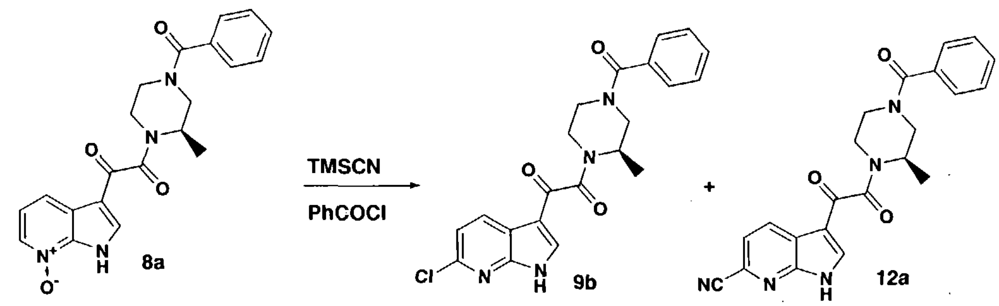
11

Compound **11a**: R = Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4 or 6)-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_3$: 391.18; found 391.17. HPLC retention time: 1.35 minutes (column B).

Compound **11b**: R = Ph, *(R)-N-(benzoyl)-3-methyl-N'-[(4 or 6)-phenyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{27}H_{25}N_4O_3$: 453.19; found 454.20. HPLC retention time: 1.46 minutes (column B).

Compound **11c**, R = CH=CH2, *(R)-N-(benzoyl)-3-methyl-N'-[(4 or 6)-vinyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+Na)^+$ calcd for $C_{23}H_{22}N_4NaO_3$: 425.16; found 425.23. HPLC retention time: 1.12 minutes (column A).

6) Nitrile Substitution and Chlorination (equation 5, Scheme 5)



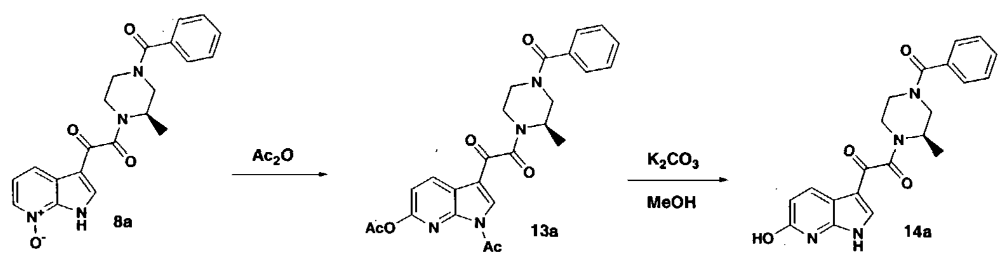
Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(6-chloro-7-azaindol-3-yl)-oxoacetyl]-piperazine **9b** *and (R)-N-(benzoyl)-3-methyl-N'-[(6-cyano-7-azaindol-3-yl)-oxoacetyl]-piperazine* ***12a:*** *N*-oxide **8a** (0.20 g, 0.51 mmol) was suspended in 20 ml of dry THF, to which TMSCN (0.3 g, 3.0 mmol) and BzCl (0.28 g, 2.0 mmol) were added. The reaction mixture was stirred at room temperature for 2 hours, and then heated at reflux for 5 hours. After cooling, the mixture was poured into 100 ml of saturated $NaHCO_3$ and the aqueous phase extracted with EtOAc (3 x 50 ml). The organic phase was combined and concentrated under vacuum to give a residue, which was diluted with methanol and purified using a Shimadzu automated preparative HPLC System to give compound **12a** (42 mg, 20%) and compound **9b** (23 mg, 11%).

Characterization of compounds **9b** and **12a**:

Compound **9b**, *(R)-N-(benzoyl)-3-methyl-N'-[(6-chloro-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (m, 2H), 7.42 (m, 6H), 5.00-2.80 (m, 7H), 1.19 (b, 3H); ^{13}C NMR (125 MHz, DMSO-d_6). δ 185.8, 170.0, 165.1, 147.9, 145.1, 137.4, 135.4, 132.2, 129.5, 128.3, 126.8, 118.6, 116.1, 111.8, 49.3, 47.2, 44.2, 15.6, 14.5. MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$: 411.12; found 411.09. HPLC retention time: 1.43 minutes (column A).

Compound **12a**, *(R)-N-(benzoyl)-3-methyl-N'-[(6-cyano-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (m, 2H), 7.86 (s, 1H), 7.42 (m, 5H), 4.80-2.80 (m, 7H), 1.22 (b, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.7, 170.0, 164.8, 148.5, 140.9, 135.3, 130.3, 129.5, 128.3, 126.8, 126.2, 123.0, 120.4, 118.0, 111.8, 49.4, 47.3, 44.2, 15.6, 14.5. MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{20}N_5O_3$: 402.16; found 402.13. HPLC retention time: 1.29 minutes (column A).

7) Hydroxylation (equation 6, Scheme 5)



Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(1-acetyl-6-acetoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine ***13a***: 20 mg of 7-azaindole piperazine diamide N-oxide **8a** was dissolved in 5 ml of acetic anhydride (Ac_2O). The reaction mixture was heated at reflux for 8 hours. After cooling, the solvents were removed under vacuum to give product **13a**, which was pure enough for further reactions.

Characterization of compound **13a**:

Compound **13a**, *(R)-N-(benzoyl)-3-methyl-N'-[(1-acetyl-6-acetoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.67 (m, 2H), 7.47 (s, 5H), 7.27 (d, 1H, J = 8.34 Hz), 4.90-2.80 (m, 7H), 2.09 (s, 6H), 1.30 (b, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 187.0, 170.8, 169.0, 168.6, 164.9, 155.3, 136.5, 134.7, 134.2, 133.2, 130.0, 129.8, 127.5, 118.9, 115.4, 113.8, 50.3, 45.4, 41.3, 36.3, 25.5, 20.5, 16.0, 14.8.

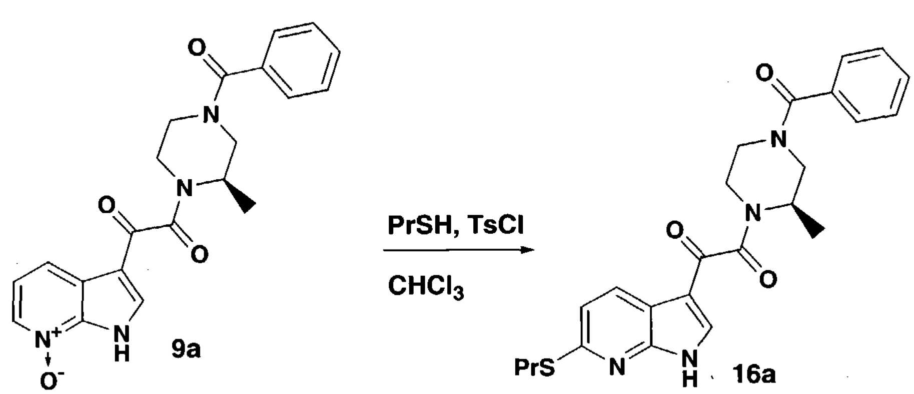
MS m/z: $(M+Na)^+$ calcd for $C_{25}H_{24}N_4O_6Na$: 499.16; found 499.15. HPLC retention time: 1.46 minutes (column B).

*Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(6-hydroxyl-7-azaindol-3-yl)-oxoacetyl]-piperazine **14a***: The crude compound **13a** and an excess of K_2CO_3 (100 mg) were mixed in MeOH and H_2O (1:1). The reaction mixture was stirred for 8 hours. The MeOH was removed under vacuum, the aqueous phase extracted with EtOAc (3 x 10ml) and the organic layers combined and concentrated. The crude product was purified using a Shimadzu automated preparative HPLC System to give compound 1 mg of **14a** (5% from compound **8a**).

Characterization of compound **14a**:

Compound **14a**, *(R)-N-(benzoyl)-3-methyl-N'-[(6-hydroxyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS m/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.12. HPLC retention time: 1.13 minutes (column A).

8) Thiol formation (equation 7, Scheme 5)



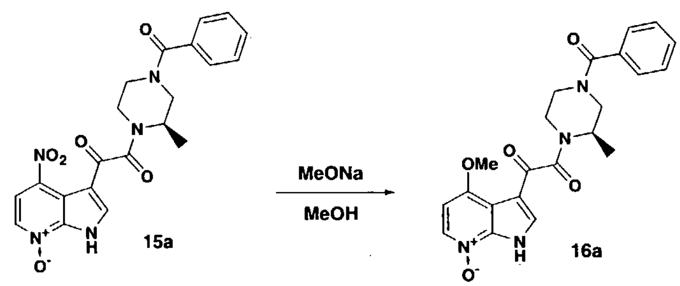
*Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(6-propylthio-7-azaindol-3-yl)-oxoacetyl]-piperazine **17f***. To an solution of 100 mg of compound **9a** in 10 ml of $CHCl_3$ was added TsCl (63 mg), and the

solution was stirred for 5 minutes. Then, 2 ml of propylthiol was added and the reaction mixture was stirred for 8 hours. After concentration, the crude product was purified using a Shimadzu automated preparative HPLC System to give compound 1.4 mg of **17f**.

Characterization of compound **17f**:

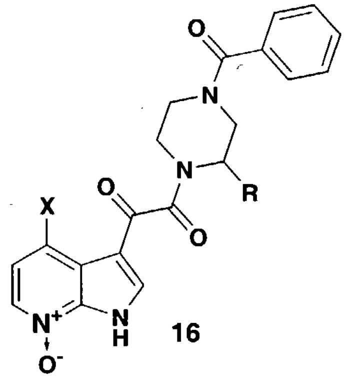
Compound **17f**, *(R)-N-(benzoyl)-3-methyl-N'-[(6-propylthiol-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{27}N_4O_3S$: 451.18; found 451.09. HPLC retention time: 1.45 minutes (column A).

9) Displacement of Nitro Group (equation 11, Scheme 6)



*Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine **16a***: 100 mg of crude compound **15a** from the previous step was dissolved in 6 ml of 0.5M MeONa in MeOH. The reaction mixture was refluxed for 8 hours, and the solvent removed under vacuum to afford a mixture including product **16a** and other inorganic salts. This mixture was used in the next step without further purification. A small portion of the crude mixture was purified using a Shimadzu automated preparative HPLC System to give 5 mg of compound **16a**.

Characterization of compounds **16** with the following sub-structure:



16

Compound **16a**, X = OMe, R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_5$ 423.17, found 423.04. HPLC retention time: 0.97 minutes (column A).

Compound **16f**, X = OMe, R = *(S)*-Me, *(S)-N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_5$ 423.17, found 423.02.

Compound **16g**, X = OMe, R = Me, *N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_5$ 423.17, found 423.03.

Compound **16b**, X = OCH_2CF_3, , R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-(2,2,2-trifluoroethoxy)-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.44 (b, 1H), 8.30 (m, 1H), 7.50 (b, 5H), 7.14 (b, 1H), 4.90-3.10 (m, 9H), 1.30 (m, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{23}H_{22}F_3N_4O_5$: 491.15; found 491.16. HPLC retention time: 1.17 minutes (column A).

Compound **16c**, X = $OCH(CH_3)_2$, , R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-(1-methylethoxy)-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.48 (s, 1H), 8.24 (m, 1H), 7.46 (m, 5H), 7.13 (s, 1H), 5.03-3.00 (m, 8H), 1.49-1.15 (m, 9H). MS *m/z*:

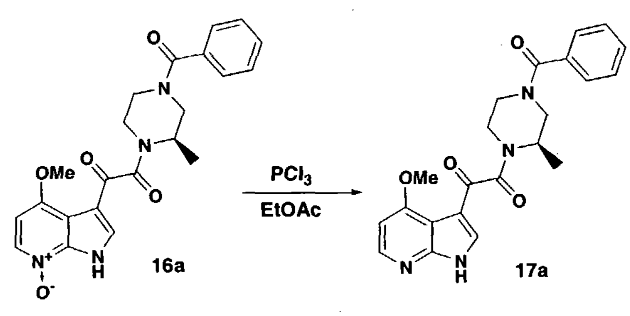
$(M+H)^+$ calcd for $C_{24}H_{27}N_4O_5$: 451.20; found 451.21. HPLC retention time: 1.14 minutes (column A).

Compound **16d**, X = OCH_2CH_3, , R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-ethoxy-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_5$: 437.18; found 437.13. HPLC retention time: 1.08 minutes (column A).

Compound **16e** X = $SCH_2CH_2CH_3$, , R = *(R)*-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-propylthio-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (m, 2H), 7.45 (m, 5H), 7.25 (s, 1H), 4.90-3.00 (m, 9H), 1.81 (b, 2H), 1.30 (m, 6H). MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{27}N_4O_4S$: 467.18; found 467.14. HPLC retention time: 1.30 minutes (column A).

Compound **16h**, X = NHMe, , R = (R)-Me, *(R)-N-(benzoyl)-3-methyl-N'-[(4-methylamino-7-oxide-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{24}N_5O_4$: 422.18; found 422.09. HPLC retention time: 1.19 minutes (column A).

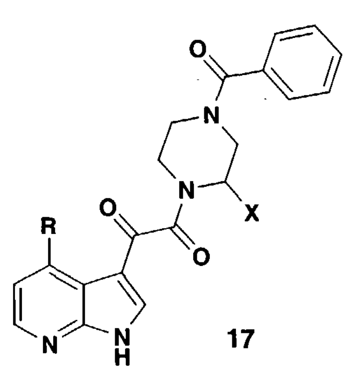
10) Reduction of N-Oxide (equation 12, Scheme 6)



Preparation of (R)-*N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine* ***17a***: 48 mg of crude **16a** was suspended in 30 ml of ethyl acetate at room temperature. 1 ml of PCl_3 was added and the reaction was mixture stirred for 8 hours. The reaction

mixture was poured into ice cooled 2N NaOH solution with caution. After separating the organic layer, the aqueous phase was extracted with EtOAc (6 x 80 ml). The organic layers were combined, and concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to give 38 mg of compound **17a**.

Characterization of compounds **17** with the following sub-structure:



17

Compound **17a**, R = Ome, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, CD_3OD) δ 8.24 (d, 1H, J = 5.7 Hz), 8.21(m, 1H), 7.47 (s, 5H), 6.90 (d, 1H, J = 5.7 Hz), 4.71-3.13 (m, 10H), 1.26 (b, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 185.3, 172.0, 167.2, 161.2, 150.7, 146.6, 135.5, 134.8, 129.9, 128.3, 126.7, 112.8, 106.9, 100.6, 54.9, 50.2, 48.1, 45.1, 14.5, 13.8. MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_4$: 407.17; found 407.19. HPLC retention time: 1.00 minutes (column A).

Compound **17d**, R = Ome, X = *(S)*-Me, *(S)-N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_4$: 407.17; found 407.03.

Compound **17e**, R = Ome, X = Me, *N-(benzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_4$: 407.17; found 407.03.

Compound **17b**, R = OCH_2CF_3, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-(2,2,2-trifluoroethoxy)-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.33 (s, 1H), 8.19 (m, 1H), 7.45 (m, 5H), 7.05 (s, 1H), 4.90-3.00 (m, 9H), 1.29 (b, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.7, 174.0, 168.3, 162.0, 151.0, 146.1, 138.5, 136.4, 131.4, 130.0, 128.2, 114.8, 109.5, 103.6, 67.2, 66.9, 52.0, 47.0, 16.4, 15.3. MS *m*/z: $(M+H)^+$ calcd for $C_{23}H_{22}F_3N_4O_4$: 475.16; found 475.23. HPLC retention time: 1.22 minutes (column A).

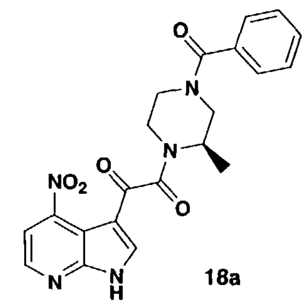
Compound **17c**, R = $OCH(CH_3)_2$, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-(1-methylethoxy)-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.42 (s, 1H), 8.24 (m, 1H), 7.47 (m, 5H), 7.21 (s, 1H), 5.20-3.00 (m, 8H), 1.51 (b, 6H), 1.22 (b, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.4, 173.6, 167.9, 166.1, 145.3, 141.4, 138.2, 136.4, 131.5, 129.7, 128.2, 113.9, 111.4, 104.0, 75.5. 54.4, 53.7, 51.8, 46.9, 22.1, 16.4, 15.3. MS *m*/z: $(M+H)^+$ calcd for $C_{24}H_{27}N_4O_4$: 435.20; found 435.20. HPLC retention time: 1.15 minutes (column A).

Compound **17m**, R = OCH_2CH_3, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-ethoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_4$: 421.19; found 421.13. HPLC retention time: 1.13 minutes (column A).

Compound **17g**, R = $SCH_2CH_2CH_3$, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-propylthio-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{24}H_{27}N_4O_4S$: 451.18; found 451.13. HPLC retention time: 1.50 minutes (column A).

Compound **17h**, R = NHMe, X = (R)-Me, (R)-*N-(benzoyl)-3-methyl-N'-[(4-methylamino-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{24}N_5O_3$: 406.19; found 406.03. HPLC retention time: 1.19 minutes (column A).

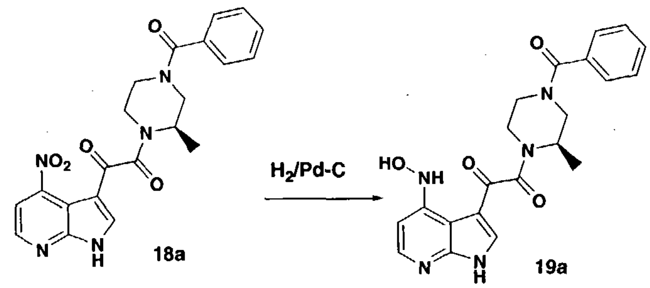
Characterization of compound **18a**



18a

Compound **18a**, (R)-*N-(benzoyl)-3-methyl-N'-[(4-nitro-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (300 MHz, CD_3OD) δ 8.58 (s, 1H), 8.53 (m, 1H), 7.64 (s, 1H), 7.47 (s, 5H), 4.90-3.00 (m, 7H), 1.30 (b, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 184.1, 172.1, 165.6, 151.9, 149.6, 145.5, 139.4, 134.8, 129.7, 128.4, 126.7, 111.6, 111.2, 107.4, 53.7, 48.4, 45.9, 15.0, 13.7. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}N_5O_5$: 422.15; found 422.09. HPLC retention time: 1.49 minutes (column B).

11) Reduction of Nitro to Hydoxylamine Group (equation 14, Scheme 6)



18a

19a

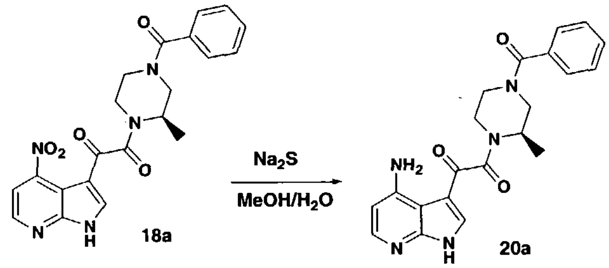
Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-hydroxylamino-7-azaindol-3-yl)-oxoacetyl]-piperazine ***19a***: 10 mg of Pd (10% on activated carbon) was added to a solution of compound **18a** (48 mg, 0.11 mmol) in methanol (10 ml) under an atmosphere of hydrogen. The reaction mixture was stirred for 8 hours at room temperature. After filtration, the

filtrate was concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to give compound **19a** (7.9 mg, 17%).

Characterization of compound **19a**:

Compound **19a**, *(R)-N-(benzoyl)-3-methyl-N'-[(4-hydroxylamino-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{22}N_5O_4$: 408.17; found 408.21. HPLC retention time: 1.03 minutes (column A).

12) Reduction of Nitro to Amine Group (equation 15, Scheme 6)



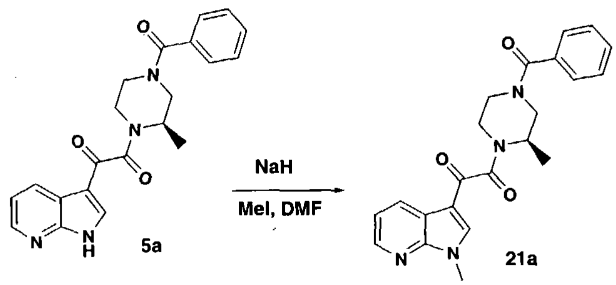
Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-amino-7-azaindol-3-yl)-oxoacetyl]-piperazine ***20a:*** 114 mg of $Na_2S.2H_2O$ (1 mmol) was added to a solution of compound **18a** (20 mg, 0.048mmol) in MeOH (5 ml) and H_2O (5 ml). The reaction mixture was heated at reflux for 8 hours. After cooling, the reaction mixture was concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to give 4 mg of compound **20a** (21.3%).

Characterization of compound **20a**:

Compound **20a**, *(R)-N-(benzoyl)-3-methyl-N'-[(4-amino-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^1H NMR (500 MHz, CD_3OD) δ 8.16 (m, 1H), 8.01(d, 1H, J = 8.1 Hz), 7.47 (m, 5H), 6.66 (s, 1H), 4.90-3.00 (m, 7H),

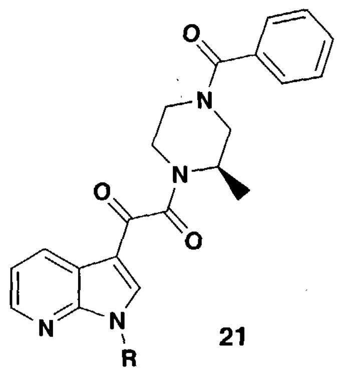
1.30 (b, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{22}N_5O_3$: 392.17; found 392.14. HPLC retention time: 0.96 minutes (column A).

13) Alkylation of the nitrogen atom at position 1 (equation 16, Scheme 7)



Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(1-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine ***21a***: NaH (2 mg, 60% pure, 0.05 mmol) was added to a solution of compound **5a** (10 mg, 0.027 mmol) in DMF. After 30 minutes, MeI (5 mg, 0.035 mmol) was injected into the mixture *via* syringe. The reaction mixture was stirred for 8 hours at room temperature and quenched with methanol. The mixture was partitioned between ethyl acetate (2 ml) and H_2O (2 ml). The aqueous phase was extracted with EtOAc (3 x 2 ml). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a crude product which was purified using a Shimadzu automated preparative HPLC System to give compound **21a** (2.5 mg, 24%).

Characterization of compound **21** with the following sub-structure:

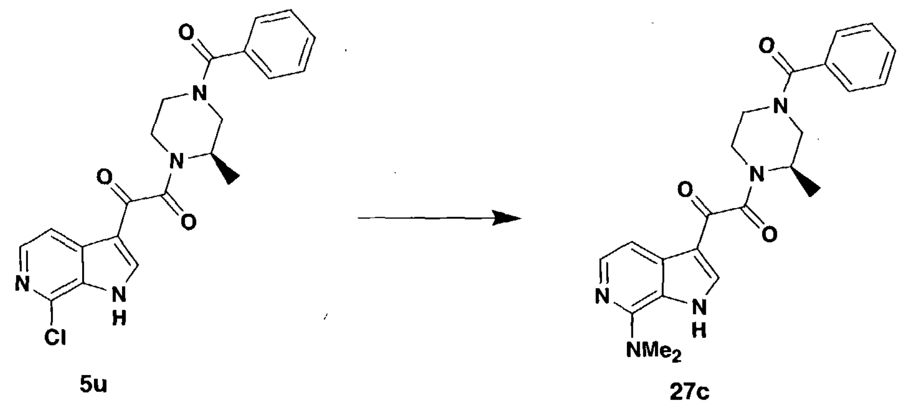


21

Compound **21a**, R = Me, *(R)-N-(benzoyl)-3-methyl-N'-[(1-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.56 (b, 1H), 8.42 (s, 1H), 8.30 (m, 1H), 7.47 (m, 6H), 4.90-3.00 (m, 7H), 3.96 (s, 3H), 1.28 (b, 3H). MS *m/z*: $(M+Na)^+$ calcd for $C_{22}H_{22}N_4O_3Na$: 413.16; found 413.15. HPLC retention time: 1.47 minutes (column B).

Compound **21b**, R = CH_2-CH=CH_2, *(R)-N-(benzoyl)-3-methyl-N'-[(1-allyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (m, 3H), 7.44 (m, 6H), 6.08 (m, 1H) , 5.22 - 3.06 (m, 11H), 1.27 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 184.2, 184.1, 170.8, 165.0, 146.7, 143.5, 137.9, 133.8, 131.4, 129.2, 128.8, 127.3, 125.6, 117.9, 117.4, 116.3, 110.3, 50.4, 49.7, 49.1, 45.7, 44.0, 41.0, 39.6, 34.8, 14.0, 12.8, . MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{25}N_4O_3$: 417.19; found 417.11. HPLC retention time: 1.43 minutes (column A).

14) Group transfer reactions from halide (equation 18, Scheme 8)

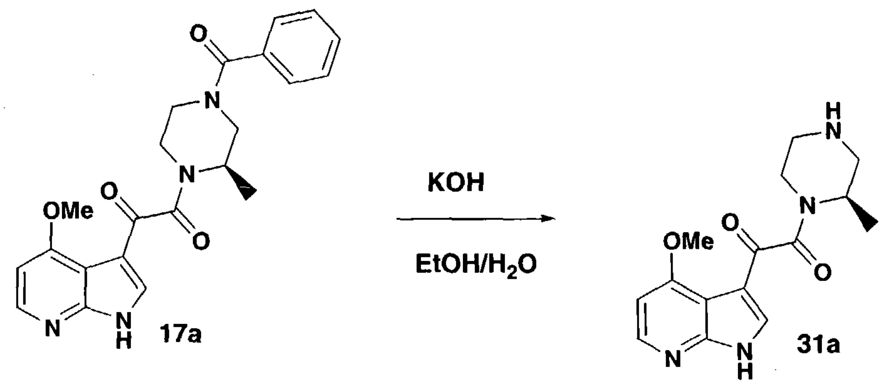


Preparation of *(R)-N-(benzoyl)-3-methyl-N'-[(7-dimethylamino-6-azaindol-3-yl)-oxoacetyl]-piperazine* **27c**: A mixture of compound **5u** (50 mg) and 4 ml of dimethylamine (40% in water) was heated to 150^{O}C in sealed tube for 18 hours. The solvents were then removed under vaccum and the residue was purified using Shimadzu automated preparative HPLC System to give 10 mg of compound **27c**.

Characterization of compound **27c**:

Compound **27c**, *(R)-N-(benzoyl)-3-methyl-N'-[(7-dimethylamino-6-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{23}H_{26}N_5O_3$ 420.20, found 420.16. HPLC retention time: 1.13 minutes (column A).

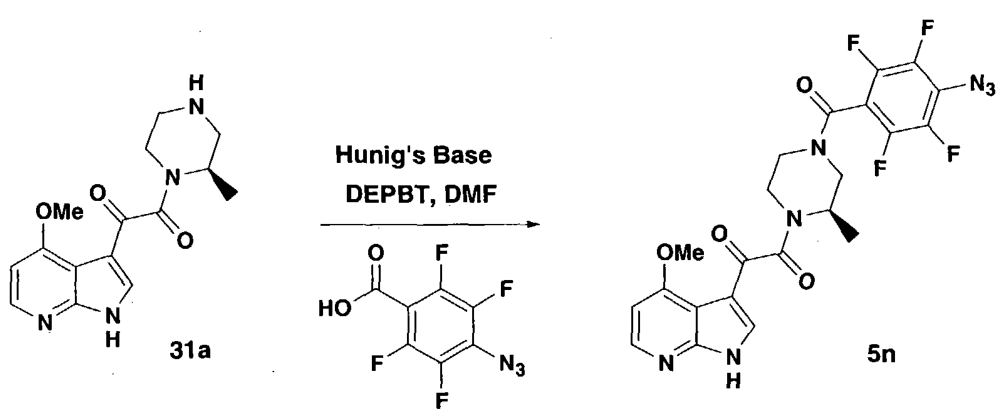
15) Modification of benzoyl moiety(equation 26, Schem 11)



Hydrolysis of benzoyl amide, preparation of *(R)-2-methyl-N-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine* **31a**: Compound **17a** (0.9 g) and KOH (2.0 g) were mixed in a solution of EtOH (15 ml) and water (15 ml). The reaction was refluxed for 48 hours. Solvents were removed under vaccum and the resulting residue was purified by silica gel column chromatography (EtOAc / Et_3N = 100 : 1 to 3 :1) to afford 0.6 g of compound **31a**.

Characterization of compound **31a**:

Compound **31a**, *(R)-2-methyl-N-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{15}H_{19}N_4O_3$ 303.15, found 303.09. HPLC retention time: 0.29 minutes (column A).



Diamide formation: *Preparation of (R)-N-(4-azido-2,3,5,6-tetra-fluorobenzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine* ***5n***: Amine **31a** (0.15 g), 4-azido-2,3,5,6-tetrafluorobenzoic acid (0.12 g), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (0.15 g) and Hunig's Base (0.5 ml) were combined in 5 ml of DMF. The mixture was stirred at room temperature for 8 hours. Solvents were then removed under vaccum and the residue was purified using Shimadzu automated preparative HPLC System to give 10 mg of compound **5n**.

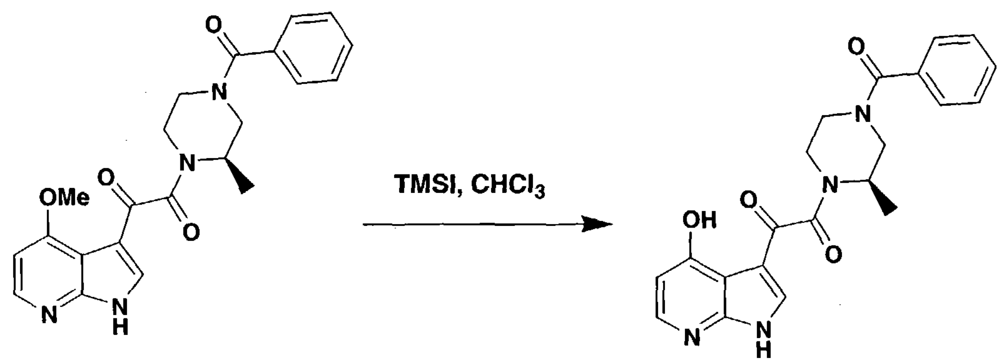
Characterization of compound **5n**:

Compound **5n**, *(R)-N-(4-azido-2,3,5,6-tetra-fluorobenzoyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{18}F_4N_7O_4$ 520.14, found 520.05. HPLC retention time: 1.42 minutes (column A).

Compound **5af**, Ar = 4, 5-dibromophenyl, *(R)-N-(3, 5-dibromobenzyl)-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{21}Br_2N_4O_4$ 562.99, found 562.99. HPLC retention time: 1.54 minutes (column A).

Compound **5ag**, Ar = 4-[3-(trifluoromethyl)-3H-diazirin-3-yl]phenyl, *(R)-N-[4-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzyl]-3-methyl-N'-[(4-methoxy-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{22}F_3N_6O_4$ 515.17, found 515.02. HPLC retention time: 1.55 minutes (column A).

New Equation:



Preparation of (R)-N-(benzoyl)-3-methyl-N'-[(4-hydroxyl-7-azaindol-3-yl)-oxoacetyl]-piperazine ***5ah***: The crude compound **17a** (100 mg) and an excess of TMSI (0.25 ml) were mixed in $CHCl_3$. The reaction mixture was stirred for 6 days. The solvent was removed under vacuum, he crude product was purified using a Shimadzu automated preparative HPLC System to give compound 4.4 mg of **5ah**.

Characterization of compound **5ah**:

Compound **5ah**, *(R)-N-(benzoyl)-3-methyl-N'-[(4-hydroxyl-7-azaindol-3-yl)-oxoacetyl]-piperazine*: MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_4$: 393.16; found 393.11. HPLC retention time: 1.46 minutes (column B).

Alternate procedures useful for the synthesis of Compound 39

Preparation of 5,7-dibromo-4-methoxy-7-azaindole **36**: Vinylmagnesium bromide (0.85 M in THF, 97.7 mL, 83.0 mmol) was added over 30 min. to a stirring solution of 2,6-dibromo-3-methoxy-5-nitropyridine (7.4 g, 23.7 mmol) in THF (160 mL) at –75 °C. The solution was stirred 1h at –75 °C, overnight at –20 °C, recooled to –75 °C and quenched with saturated aqueous NH_4Cl (~100 mL). The reaction mixture was allowed to warm to rt, washed with brine (~100 mL) and extracted with Et_2O (150 mL) and CH_2Cl_2 (2 x 100 mL). The combined

organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, 3:1 hexanes/EtOAc) to yield 5,7-dibromo-4-methoxy-7-azaindole **36** (1.10 g, 3.60 mmol, 15%) as a pale yellow solid.

Characterization of **36**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.41 (dd, J = 3.1, 2.8 Hz, 1H), 6.69 (d, J = 3.1, 2.2 Hz, 1H), 4.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 133.7, 128.8, 127.5, 120.2, 115.6, 101.9, 60.7. MS m/z $(M+H)^+$ calcd for $C_8H_7Br_2N_2O$: 304.88; found 304.88. HPLC retention time: 1.31 minutes (column A).

Preparation of 4-methoxy-7-azaindole **37**: A solution of 5,7-Dibromo-4-methoxy-7-azaindole **36** (680 mg, 2.22 mmol), 5% Pd/C (350 mg, 0.17 mmol) and hydrazine (2.5 mL, 80 mmol) in EtOH was heated at reflux for 1 h. The reaction mixture was allowed to cool to rt, filtered through celite and the filtrate concentrated. Aqueous NH_4OH (11% in H_2O, 45 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to yield 4-methoxy-7-azaindole **37** (290 mg, 1.95 mmol, 88%) as an orange solid.

Characterization of **37**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.52 (s, 1H), 7.88 (s, 1H), 7.30 (d, J = 2.9 Hz, 1H), 6.69 (d, J = 2.9 Hz, 1H), 4.03 (s, 3H). MS m/z $(M+H)^+$ calcd for $C_8H_9N_2O$: 149.06; found 148.99. HPLC retention time: 0.61 minutes (column A).

Preparation of **38**: Aluminum trichloride (67 mg, 0.50 mmol) was added to a solution of 4-methoxy-6-azaindole (15 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) and stirred at rt for 30 min. Methyl chlorooxacetate (0.020 mL, 0.21 mmol) was added and the reaction mixture was stirred overnight. The reaction was quenched with MeOH (0.20 mL), stirred 5 h and filtered (flushing with CH_2Cl_2). The filtrate was washed with saturated

aqueous NH_4OAc (2 x 10 mL) and H_2O (10 mL) and concentrated to yield **38** (5 mg) as a yellow solid.

Characterization of **38**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.36 (s, 1H), 8.02 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H). MS *m/z* $(M+H)^+$ calcd for $C_{11}H_{10}N_2O_4$: 235.06; found 234.96. HPLC retention time: 0.63 minutes (column A).

Preparation of N-benzoyl-N'-[(2-carboxaldehyde-pyrrole-4-yl)-oxoacetyl]-piperazine **41**: A solution of ethyl 4-oxoacetyl-2-pyrrolecarboxaldehyde **40** (17.0 g, 87.1 mmol) in 25 mL of KOH (3.56 M in H_2O, 88.8 mmol) and EtOH (400 mL) was stirred 2h. The white precipitate that formed was collected by filtration, washed with EtOH (~30 mL) and Et_2O (~30 mL) and dried under high vacuum to yield 15.9 g of potassium 2-pyrrolecarboxaldehyde-4-oxoacetate as a white solid that was used without further purification. A solution of potassium 2-pyrrolecarboxaldehyde-4-oxoacetate (3.96 g, 19.3 mmol), N-benzoylpiperazine hydrochloride (4.54 g, 19.7 mmol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (5.88 g, 19.7 mmol) and triethylamine (3.2 mL, 23 mmol) in DMF (50 mL) was stirred 1d. The reaction mixture was filtered into H_2O (300 mL), extracted with CH_2Cl_2 (3 x 200 mL) and the combined organics were concentrated on a rotary evaporator to remove the CH_2Cl_2. The crude material (still in DMF) was then diluted with H_2O (200 mL) and allowed to recrystallize for 48 h. The solid was then collected by filtration and dried under high vacuum (P_2O_5) to yield N-benzoyl-N'-[(2-carboxaldehyde-pyrrole-4-yl)-oxoacetyl]-piperazine **41** (3.3 g, 9.7 mmol, 45% over two steps) as a light yellow solid. No further purification was required.

Characterization of **41**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 9.63 (s, 1H), 7.82 (s, 1H), 7.51-7.34 (m, 6H), 4.05-3.35 (m, 8H). MS *m/z* $(M+H)^+$

calcd for $C_{18}H_{18}N_3O_4$: 340.12; found 340.11. HPLC retention time: 1.04 minutes (column A).

Preparation of **42**: N-benzoyl-N'-[(2-carboxaldehyde-pyrrole-4-yl)-oxoacetyl]-piperazine **41** (3.3 g, 9.7 mmol) was stirred as a slurry in EtOH (100 mL) for 15 min., cooled to 0 $^{\circ}$C and then reacted with glycine methyl ester hydrochloride (3.66 g, 29.2 mmol), triethylamine (1.50 mL, 11 mmol) and sodium cyanoborohydride (672 mg, 10.7 mmol). The reaction mixture was allowed to warm to rt, stirred 24 h and poured into ice (~400 mL). The solution was extracted with EtOAc (3 x 300 mL) and the combined organics were washed with brine (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (SiO_2, 9:1 EtOAc/MeOH, R_f = 0.2) to yield **42** (2.4 g, 5.8 mmol, 60%) as a white solid.

Characterization of **42**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.49 (s, 1H), 7.58-7.32 (m, 5H), 6.50 (s, 1H), 3.90-3.35 (m, 8H), 3.81 (s, 2H), 3.74 (s, 3H), 3.40 (s, 2H). MS *m/z* $(M+H)^+$ calcd for $C_{21}H_{25}N_4O_5$: 413.17; found 413.17. HPLC retention time: 0.84 minutes (column A).

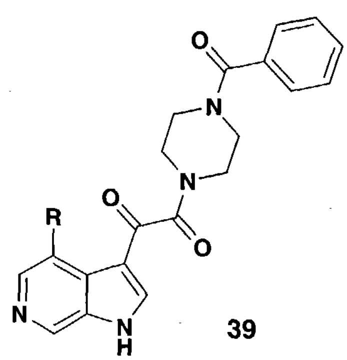
Preparation of **43**: Methyl ester **42** (485 mg, 1.17 mmol) and K_2CO_3 (325 mg, 2.35 mmol) in MeOH (6 mL) and H_2O (6 mL) were stirred at rt for 3h. The reaction mixture was then quenched with concentrated HCl (0.40 mL) and concentrated under high vacuum. Part of the solid residue (200 mg, 0.37 mmol) was added to a stirring solution of P_2O_5 (400 mg, 1.4 mmol) in methanesulfonic acid (4.0 g, 42 mmol) (which had already been stirred together at 110 $^{\circ}$C for 45 min.) at 110 $^{\circ}$C and stirred for 15 min. The reaction mixture was poured over crushed ice (~20 g), stirred 1 h, basified with K_2CO_3 (5.0 g, 38 mmol), diluted with CH_2Cl_2 (20 mL), and benzoyl chloride (1.0 mL, 8.5 mmol) and stirred 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were dried (Na_2SO_4) and concentrated under reduced pressure.

The residue was purified by preparative thin layer chromatography (SiO_2, EtOAc, R_f = 0.5) to yield **43** (101 mg g, 0.21 mmol, 57%) as an off white solid.

Characterization of **43**: MS *m/z* $(M+H)^+$ calcd for $C_{27}H_{24}N_4O_5$: 485.17; found 485.07. HPLC retention time: 1.15 minutes (column A).

Preparation of **39**. R = OMe, *N-(benzoyl)-N'-[(4-methoxy-6-azaindol-3-yl)-oxoacetyl]-piperazine*:

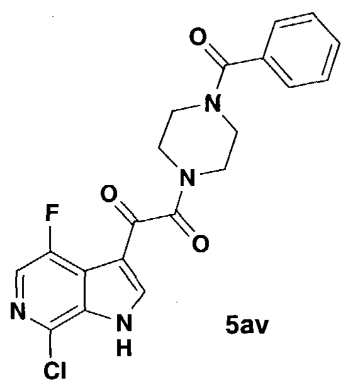
In a flask affixed with a Dean-Stark trap, p-toluenesulfonic acid hydrate (55 mg, 0.29 mmol) and benzene (5 mL) were heated to reflux for 1 h. The solution was cooled to rt and reacted with 2,2-dimethoxypropane (0.10 mL, 0.81 mmol) and **43** (46 mg, 0.095 mmol). The reaction mixture was stirred 1 h, diluted with CH_2Cl_2 (2 mL), stirred 30 min. and then oxidized with tetrachlorobenzoquinone (150 mg, 0.61 mmol) and stirred overnight. The reaction mixture was poured into 5% aqueous NaOH (20 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to preparative thin layer chromatography (Et_2O), the baseline material was extracted and resubjected to preparative thin layer chromatography (SiO_2, 9:1 EtOAc/MeOH, R_f = 0.15) to yield **39** (3 mg, 0.008 mmol, 6%) as a white solid.



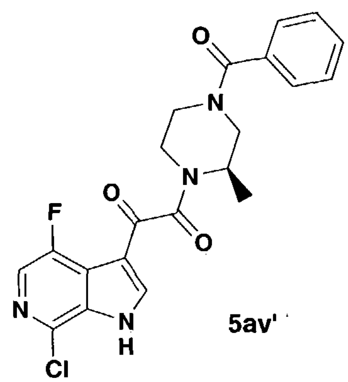
39

Compound **39**, R = OMe, *N-(benzoyl)-3-methyl-N'-[(4-methoxy-6-azaindol-3-yl)-oxoacetyl]-piperazine*:

Characterization of **39**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.49 (s, 1H), 8.35 (s, 1H), 7.98 (s, 1H), 7.53-7.38 (m, 5H), 4.02 (s, 3H), 3.97-3.42 (m, 8H). MS *m/z* $(M+H)^+$ calcd for $C_{21}H_{23}N_4O_5$: 393.15; found 393.13. HPLC retention time: 0.85 minutes (column A).



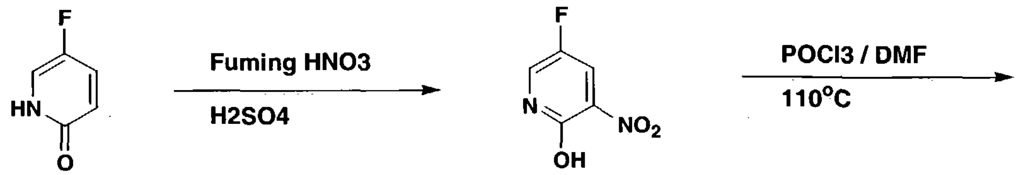
5av



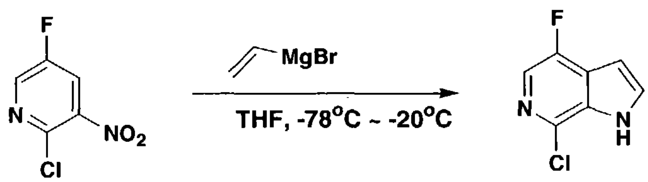
5av'

Preparation of **5av** *N-(benzoyl)-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine* and **5 av'***(R)-N-(benzoyl)-3-methyl-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine*

It should be noted that 2-chloro-5-fluoro-3-nitro pyridine may be prepared by the method in example 5B of reference 59 Marfat et.al. The scheme below provides some details which enhance the yields of this route. The Bartoli chemistry in Scheme 1 was used to prepare the aza indole **1zz** which is also detailed below.



zz1'　　zz2'



zz3'　　1zz

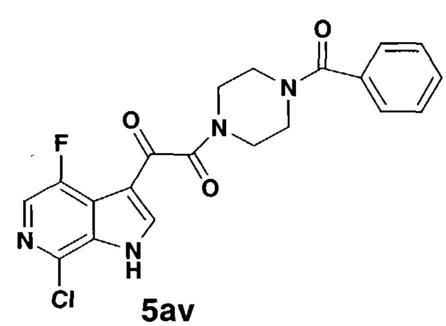
Compound **zz1'** (1.2g, 0.01mol) was dissolved in 2.7ml of sulphuric acid at room temperature. Premixed fuming nitric acid (1ml) and sulphuric acid was added dropwise at 5 - 10°C to the solution of compound **zz1'**. The reaction mixture was heated to 85°C for 1 hr, then cooled to room temperature and poured into ice (20g). The yellow solid product **zz2'** was collected by filtration, washed with water and dried in air to yield 1.01 g of compound **zz2'**.

Compound **zz2'** (500mg, 3.16mmol) was dissolved in Phosphorus oxychloride (1.7ml, 18.9mmol) and DMF (Cat) at room temperature. The reaction was heated to 110°C for 5 hr. The excess POCl3 was removed in vacuo. The residue was chromatographed on silica gel (CHCl3, 100%) to afford 176mg of product **zz3'**.

Compound **zz3'** (140mg, 0.79mmol) was dissolved in THF (5ml) and cooled to -78°C under N2. Vinyl magnesium bromide (1.0M in ether, 1.2ml) was added dropwise. After the addition was completed, the reaction mixture was kept at -20°C for about 15 hr. The reaction was then quenched with saturated NH4Cl, extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO4, concentrated and chromatographed to afford about 130mg of compound **1zz**.

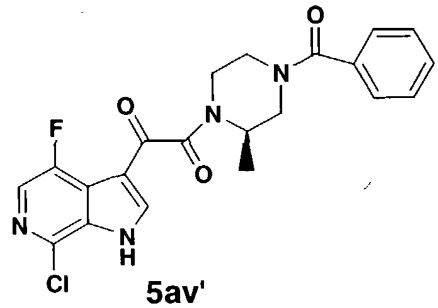
The chemistry in Scheme 3 provided the derivatives which corresponds to general formula **5** and has a 6-aza ring and R_2=F and R_4 = Cl. In particular, reaction of 2-chloro-5-fluoro-3-nitro pyridine with 3 equivalents of vinyl Magnesium bromide using the typical conditions described herein will provide 4-fluoro-7-chloro-6-azaindole in high yield. Addition of this compound to a solution of aluminum trichloride in dichloromethane stirring at ambident temperature followed 30 minutes later with chloromethyl or chloroethyl oxalate provided an ester. Hydrolysis with KOH as in the standard procedures herein provided an acid salt which reacted with piperazines **4** (for example 1-benzoyl piperazine) in the presence of DEPBT under the standard conditions described herein to provide the compound **5** described just above. The compound with the benzoyl piperazine is *N-(benzoyl)-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine* and is compound **5av.**
The compound with the (R)- methyl benzoyl piperazine is **5 av'***(R)-N-(benzoyl)-3-methyl-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine* and is compound **5av'**

Characterization of **5av** *N-(benzoyl)-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine* and **5 av'***(R)-N-(benzoyl)-3-methyl-N'-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine*



5av

^{1}H NMR (500 MHz, CD3OD): 8.40 (s, 1H), 8.04 (s, 1H), 7.46 (bs, 5H), 3.80 ~ 3.50 (m, 8H).
LC/MS: (ES+) m/z $(M+H)^+$ = 415, RT = 1.247.

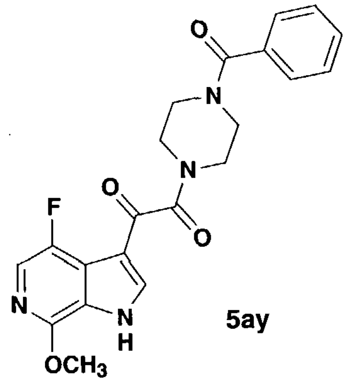


5av'

[1]H NMR (500 MHz, CD3OD): 8.42 (s, 1/2H), 8.37 (s, 1/2H), 8.03 (s, 1H), 7.71 ~ 7.45 (m, 5H), 4.72 ~ 3.05 (m, 7H), 1.45 ~ 1.28 (m, 3H).
LC/MS: (ES+) *m/z* $(M+H)^+$ = 429, RT = 1.297.

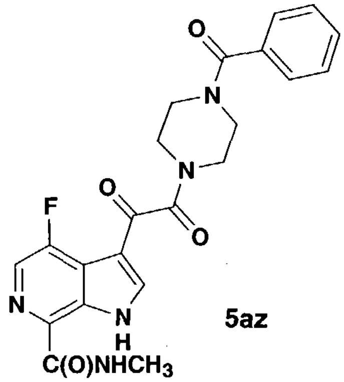
LC/MS Column: YMC ODS-A C18 S7 3.0x50mm. Start %B = 0, Final %B = 100, Gradient Time = 2 min, Flow rate = 5 ml/min. Wavelength = 220nm. Solvent A = 10% MeOH - 90% H2O - 0.1% TFA. Solvent B = 90% MeOH - 10% H2O - 0.1% TFA.

Similarly compounds 5ay, 5az, 5abc and 5abd can be made:



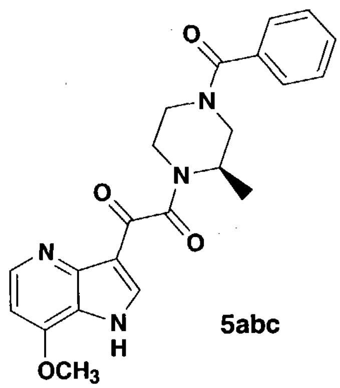
5ay

5ay *N-(benzoyl)-N'-[(4-fluoro-7-methoxy-6-azaindol-3-yl)-oxoacetyl]-piperazine*



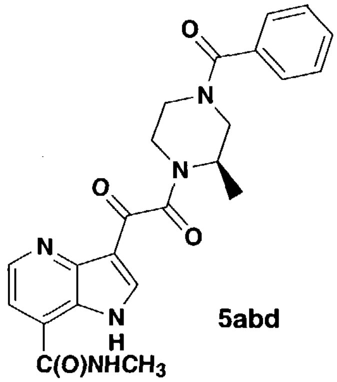
5az

5az *N-(benzoyl)-N'-[(4-fluoro-7-(N-methyl-carboxamido)-6-azaindol-3-yl)-oxoacetyl]-piperazine.*



5abc

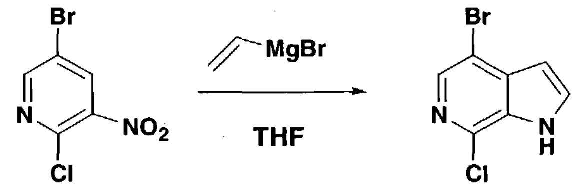
5abc*(R)-N-(benzoyl)-3-methyl-N'-[(7-methoxy-4-azaindol-3-yl)-oxoacetyl]-piperazine*



5abd

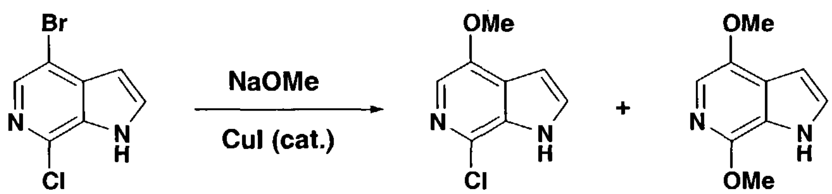
5abd *(R)-N-(benzoyl)-3-methyl-N'-[(7-(N-methyl-carboxamido)-4-azaindol-3-yl)-oxoacetyl]-piperazine.*

Compounds **5an**, **5ao** and **5ap** are described below.



1am

Compound **1am**, 4-bromo-7-chloro-6-azaindole (yellow solid)was prepared by the same method used for azaindole **1e** but the starting material employed was 5-bromo-2-chloro-3-nitropyridine. (available from Aldrich, Co.). MS *m/z*: $(M+H)^+$ calcd for $C_7H_5BrClN_2$: 230.93; found 231.15. HPLC retention time: 1.62 minutes (column B).

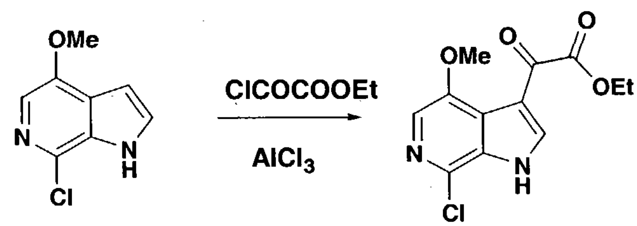


1am **1an** **1ao**

Compound **1an**, 4-methoxy-7-chloro-6-azaindole and compound **1ao**, 4,7-dimethoxy-6-azaindole: A mixture of 4-bromo-7-chloro-6-azaindole (1 g), CuI (0.65 g) and NaOMe (4 ml, 25%) in MeOH (16 ml) was heated at 110 – 120°C for 16 hours in a sealed tube. After cooling to ambient temperature, the reaction mixture was neutralized with 1N HCl to achieve pH7. The aqueous solution was extracted with EtOAc (3 x 30ml). Then the combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford a residue, which was purified by silica gel (50 g) chromatography using 1:7 EtOAc : hexane as the eluent. (Column dimension: 20mm x 30 cm) to give 0.3 g of 4-methoxy-7-chloro-6-azaindole (white solid) and 0.1 g of 4,7-dimethoxy-6-azaindole (white solid).

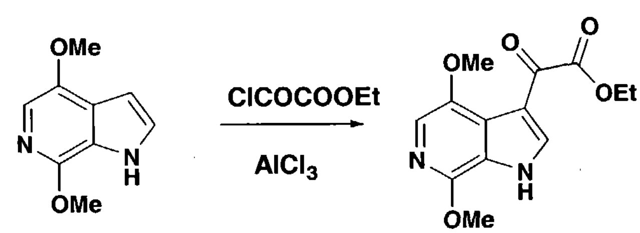
Compound **1an**, 4-methoxy-7-chloro-6-azaindole. MS *m*/z: $(M+H)^+$ calcd for $C_8H_8ClN_2O$: 183.03; found 183.09. HPLC retention time: 1.02 minutes (column B).

Compound **1ao**, 4,7-dimethoxy-6-azaindole. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.63 (m, 1H), 4.14 (s, 3H), 3.95 (s, 3H). MS *m*/z: $(M+H)^+$ calcd for $C_9H_{11}N_2O_2$: 179.08; found 179.05. HPLC retention time: 1.36 minutes (column B).



1an **2an**

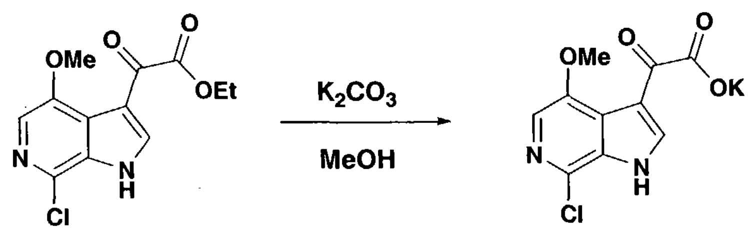
Compound **2an**, Ethyl (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method used for compound **2b** but the starting material employed was 4-methoxy-7-chloro-6-azaindole. The compound was purified by silica gel chromotography using 2:3 EtOAc : hexane as the eluent to give a yellow oil. MS *m*/z: $(M+H)^+$ calcd for $C_{12}H_{12}ClN_2O_4$: 283.05; found 283.22. HPLC retention time: 1.37 minutes (column B).



1ao **2ao**

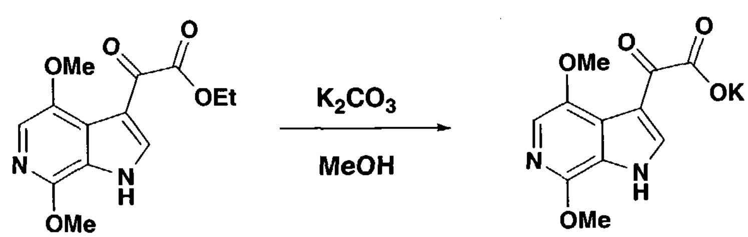
Compound **2ao**, Ethyl (4,7-dimethoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method as used for compound **2b** but the starting material employed was 4,7-dimethoxy-6-azaindole. The compound was purified by silica gel chromatography using 2 : 3 EtOAc :

Hexane as the eluent to give a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.21 (s, 1H), 7.47 (s, 1H), 4.39 (q, 2H, $d = 7.05$ Hz), 4.13 (s, 3H), 3.93 (s, 3H), 1.40 (t, 3H, $d = 7.2$ Hz). MS *m/z*: $(M+H)^+$ calcd for $C_{13}H_{15}N_2O_5$: 279.10; found 279.16. HPLC retention time: 1.28 minutes (column B).



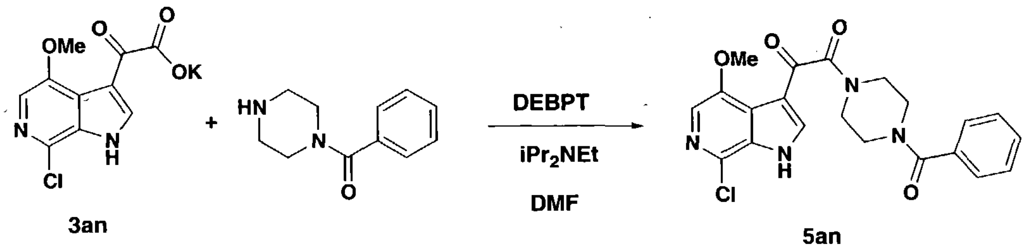
2an 3an

Compound **3an** (which was a yellow solid), Potassium (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method used to prepare compound **3a** except Ethyl (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was used as the starting material. MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3an** $(M{-}K{+}H)^+$ calcd for $C_{10}H_8ClN_2O_4$: 255.02; found 255.07. HPLC retention time: 0.74 minutes (column A).

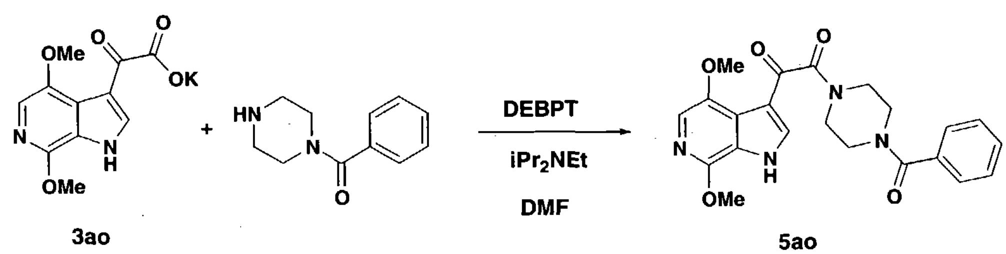


2ao 3ao

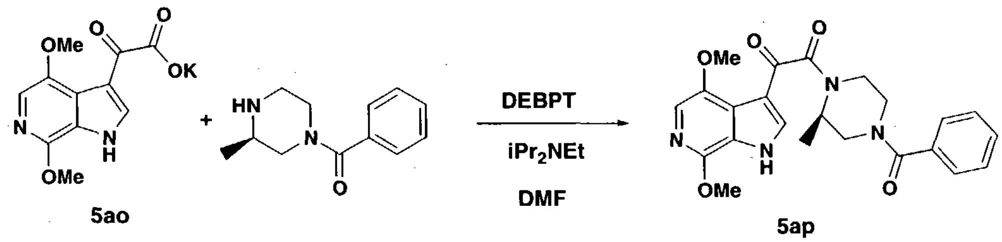
Compound **3ao** (which was a yellow solid), Potassium (4,7-dimethoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method used to prepare compound **3a** except Ethyl (4,7-dimethoxy-6-azaindol-3-yl)-oxoacetate was employed as the starting material. MS *m/z*: $(M+H)^+$ of the corresponding acid of compound **3ao** $(M{-}K{+}H)^+$ calcd for $C_{11}H_{11}N_2O_5$: 251.07; found 251.09. HPLC retention time: 0.69 minutes (column B).



Compound **5an**, N-(benzoyl)-N'-[(7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method which was used to prepare compound **5a** except that Potassium (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was employed as the starting material to give a white solid. The compound was purified by silica gel chromatography using EtOAc as the eluting solvent. MS *m*/z: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_4$: 427.12; found 427.12. HPLC retention time: 1.28 minutes (column A).



Compound **5ao**, N-(benzoyl)-N'-[(4,7-dimethoxy-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method used to prepare compound **5a** but the starting material was Potassium (4,7-dimethoxy-6-azaindol-3-yl)-oxoacetate. . The compound was purified by silica gel chromatography using EtOAc as the eluting solvent to give a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.0 (s, 1H), 8.15 (s, 1H), 7.40 (m, 6H), 4.00 (s, 3H), 3.83 (s, 3H), 3.63-3.34 (m, 8H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.5, 169.3, 166.5, 146.2, 145.7, 136.6, 135.3, 129.6, 128.4, 126.9, 122.2, 122.1, 119.2, 114.4, 56.8, 52.9, 45.5, 39.9. MS *m*/z: $(M+H)^+$ calcd for $C_{22}H_{23}N_4O_5$: 423.17; found 423.19. HPLC retention time: 1.33 minutes (column B). Anal. Calcd. For $C_{22}H_{21}N_4O_5$: C, 62.7; H, 5.02; N, 13.29. Found: C, 61.92; H, 5.41; 13.01. Melting Point: 229.5 – 232^{O}C.



Compound **5ap**, ®-N-(benzoyl)-3-methyl-N'-[(4,7-dimethoxy-6-azaindol-3-yl)-oxoacetyl]piperazine (white solid) was prepared using the same method used to prepare compound **5a** except that Potassium (4,7-dimethoxy-6-azaindol-3-yl)-oxoacetate was used as the starting material. MS *m*/z: $(M+H)^+$ calcd for $C_{23}H_{25}N_4O_5$: 437.18; found 437.24. HPLC retention time: 1.37 minutes (column B).

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical

formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Abbreviations or Alternative Names

TFA	Trifluoroacetic Acid
DMF	*N,N*-Dimethylformamide
THF	Tetrahydrofuran
MeOH	Methanol

Ether	Diethyl Ether
DMSO	Dimethyl Sulfoxide
EtOAc	Ethyl Acetate
Ac	Acetyl
Bz	Benzoyl
Me	Methyl
Et	Ethyl
Pr	Propyl
Py	Pyridine
Hunig's Base	*N,N*-Diisopropylethylamine
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DEPC	diethyl cyanophosphate
DMP	2,2-dimethoxypropane
mCPBA	*meta*-Chloroperbenzoic Acid
azaindole	1*H*-Pyrrolo-pyridine
4-azaindole	1*H*-pyrrolo[3,2-*b*]pyridine
5-azaindole	1*H*-Pyrrolo[3,2-*c*]pyridine
6-azaindole	1*H*-pyrrolo[2,3-*c*]pyridine
7-azaindole	1*H*-Pyrrolo[2,3-*b*]pyridine